Ramipril and the Development of Diabetes

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Type 2 diabetes is an important and common risk factor for the development of coronary artery disease, strokes, peripheral arterial disease, and renal and eye disease. Currently, in North America, the direct and indirect costs of diabetes and its complications exceeds $100 billion per year. This health and economic impact of diabetes is bound to increase, as the global prevalence of diabetes rises from 4.2% to 5.4% by the year 2025.

A growing amount of literature shows that the complications of diabetes can be reduced or prevented by improving glucose control, lowering blood pressure, and lipids, smoking cessation, and taking angiotensin converting enzyme (ACE) inhibitors. An even more effective approach to preventing these problems would be to prevent diabetes from developing. Whereas recent evidence from trials suggests that lifestyle modifications may reduce the risk of diabetes, the long-term adherence to such interventions has not been high. Therefore alternative strategies that are more easily implemented, safe and likely to prevent not only diabetes but also its chronic consequences, deserve to be investigated.

Recently, we demonstrated that the ACE inhibitor, ramipril, reduces myocardial infarction, strokes, deaths, and the development of diabetic nephropathy among high risk people both with and without a diagnosis of diabetes. We also observed that ramipril reduced the development of diabetes in study participants without known diabetes at randomization. This article describes this finding in detail and explores possible explanations.

Context Type 2 diabetes is a growing clinical and public health problem. Preventive efforts related to lifestyle modification are not always successful; therefore, alternative prevention strategies need to be studied.

Objective To investigate the effectiveness of ramipril, an angiotensin-converting enzyme inhibitor, in preventing diabetes among high-risk persons.

Design, Setting, and Participants The randomized, controlled Heart Outcomes Prevention Evaluation trial of 5720 patients older than 55 years without known diabetes but with vascular disease who were followed up for a mean of 4.5 years. The study included 267 hospitals in 19 countries and was conducted between 1994 and 1999.

Intervention Patients were randomly assigned to receive ramipril, up to 10 mg/d (n = 2837), or placebo (n = 2883).

Main Outcome Measure Diagnosis of diabetes determined from self-report at follow-up visits every 6 months, compared between the 2 groups.

Results One hundred and two individuals (3.6%) in the ramipril group developed diabetes compared with 155 (5.4%) in the placebo group (relative risk [RR], 0.66; 95% confidence interval [CI], 0.51-0.85, P = .001). Similar results were noted when different diagnostic criteria were used; in the ramipril group, the RR for diagnosis of diabetes and hemoglobin A1c greater than 110% was 0.60 (95% CI, 0.43-0.85), for initiation of glucose-lowering therapy, 0.56 (95% CI, 0.41-0.77), and for both, 0.51 (95% CI, 0.34-0.76). These effects were also consistently seen in several subgroups examined.

Conclusions Ramipril is associated with lower rates of new diagnosis of diabetes in high-risk individuals. Because these results have important clinical and public health implications, this hypothesis requires prospective confirmation.

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METHODS

The design of the Heart Outcomes Prevention Evaluation (HOPE) trial has been described in detail in previous publications. Briefly, individuals who were 55 years or older with no evidence of left ventricular dysfunction or heart failure and who had evidence of vascular disease or who had diabetes and 1 other risk factor were eligible as long as they had no indication or contraindication to receiving an ACE-inhibitor. The study was conducted in 267 hospitals in 19 countries from 1994 to 1999. All patients provided written informed consent.

Of 10576 eligible patients who participated in a run-in period during which they received 2.5 mg ramipril once daily for 1 week followed by matching pla
cebo for 10 to 14 days, 1035 (9.8%) were excluded from randomization (3.2% for side effects, 3.7% for lack of consent). Of the remaining 9541 patients, 3654 (38.3%) had a clinical diagnosis of diabetes and 5887 (61.7%) did not at randomization. This article focuses primarily on the latter group of patients. Of these patients, 5720 were randomized to receive up to 10 mg of ramipril once per day or equivalent placebo. One hundred sixty-seven patients who were randomized to receive a low dose (2.5 mg/day) of ramipril as part of the Study to Evaluate Carotid Ultrasound changes with Ramipril and Vitamin E (SECURE). Substudy results are not included. All patients were also randomized to receive 400 IU of vitamin E or placebo.

Follow-up visits occurred at 1 month and 6 months after randomization and then every 6 months (mean follow-up of 4.5 years). At each visit, we documented whether the diagnosis of diabetes had been made since the previous visit.

The primary outcome of this analysis is a new diagnosis of diabetes recorded on the basis of self-report. This diagnosis was made blinded to treatment allocation and, hence, is likely to be unbiased. Hemoglobin A1c (HbA1c) levels and medications used among those diagnosed as having diabetes were also recorded. The HbA1c levels were determined locally. Values higher than 110% of the upper limit of normal for each laboratory were considered to be biochemical confirmation of diabetes.

Survival curves utilizing the Kaplan Meier and log-rank procedures were used to describe and compare the results in the 2 treatment groups. Because of the factorial design, all analyses were stratified for randomization to vitamin E or placebo. Subgroup analyses were conducted using tests of interaction in the Cox regression model.

**RESULTS**

The baseline characteristics of the patients who did not have diabetes are provided in Table 1. The proportion of patients taking study ramipril or open label ACE-inhibitors in the active group was 98.3% at 2 years and 89.7% at 4 years. The proportion taking open label ACE-inhibitors in the control group was 11.6% and 27.4% respectively.

There were 102 individuals (3.6%) in the ramipril group compared with 155 (5.4%) in the placebo group (relative risk [RR], 0.66; 95% confidence interval [CI], 0.51-0.85; P<.001) who reported a new diagnosis of diabetes (Figure 1). The proportion of patients diagnosed to have diabetes and a documented glycated hemoglobin of 110% or more above the upper limit of normal (1.8% vs 3.0%; RR, 0.60; 95% CI, 0.43-0.85; P=.003), those receiving an oral glucose lowering agent or insulin (2.1% vs 3.6%; RR, 0.56; 95% CI, 0.41-0.77; P<.001). Those with all criteria (1.3% vs 2.5%; RR, 0.51; 95% CI, 0.34-0.76; P<.001) were significantly lower in the ramipril group compared with the placebo group. Vitamin E and placebo did not differ in their effect on diabetes.

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Table 2. Effect of Ramipril on the Development of Diabetes Using a Range of Criteria and Stratified by the Occurrence of Specific Events*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ramipril</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New Diabetes†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With primary event</td>
<td>9 (2.4)</td>
<td>26 (5.5)</td>
<td>0.46 (0.21-0.98)</td>
<td>.04</td>
</tr>
<tr>
<td>No primary event</td>
<td>93 (3.8)</td>
<td>129 (5.4)</td>
<td>0.69 (0.53-0.91)</td>
<td>.007</td>
</tr>
<tr>
<td>With new MA or ON</td>
<td>20 (5.6)</td>
<td>36 (8.4)</td>
<td>0.65 (0.38-1.12)</td>
<td>.12</td>
</tr>
<tr>
<td>No new MA or ON</td>
<td>82 (3.3)</td>
<td>119 (4.9)</td>
<td>0.67 (0.51-0.89)</td>
<td>.005</td>
</tr>
<tr>
<td></td>
<td>New Diabetes With Glycated Hemoglobin ≥110%, ULN‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With primary event</td>
<td>7 (1.9)</td>
<td>16 (3.4)</td>
<td>0.59 (0.24-1.43)</td>
<td>.23</td>
</tr>
<tr>
<td>No primary event</td>
<td>45 (1.8)</td>
<td>71 (3.0)</td>
<td>0.61 (0.42-0.89)</td>
<td>.009</td>
</tr>
<tr>
<td>With new MA or ON</td>
<td>10 (2.8)</td>
<td>25 (5.8)</td>
<td>0.47 (0.23-0.98)</td>
<td>.04</td>
</tr>
<tr>
<td>No new MA or ON</td>
<td>42 (1.7)</td>
<td>62 (2.5)</td>
<td>0.66 (0.45-0.98)</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>New Diabetes With Oral Agents or Insulin§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With primary event</td>
<td>5 (1.3)</td>
<td>16 (3.4)</td>
<td>0.42 (0.15-1.14)</td>
<td>.08</td>
</tr>
<tr>
<td>No primary event</td>
<td>54 (2.2)</td>
<td>89 (3.7)</td>
<td>0.58 (0.42-0.82)</td>
<td>.002</td>
</tr>
<tr>
<td>With new MA or ON</td>
<td>14 (3.9)</td>
<td>27 (6.3)</td>
<td>0.61 (0.32-1.16)</td>
<td>.13</td>
</tr>
<tr>
<td>No new MA or ON</td>
<td>45 (1.8)</td>
<td>73 (3.2)</td>
<td>0.56 (0.39-0.81)</td>
<td>.002</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval; MA, microalbuminuria; ON, overt nephropathy; ULN, upper limits of normal; and primary event, death, myocardial infarction, or stroke.
†Controlling for primary events and development of MA or ON, new diabetes with glycated hemoglobin ≥110% had a 0.67 RR (95% CI, 0.52-0.86).
‡Controlling for primary events and development of MA or ON, new diabetes with glycated hemoglobin ≥110% had a 0.62 RR (95% CI, 0.44-0.88).
§Controlling for primary events and development of MA or ON, new diabetes with patient taking glucose-lowering therapy had a 0.58 RR (95% CI, 0.42-0.79).
¶Controlling for primary events and development of MA or ON, new diabetes with elevated glycated hemoglobin or receiving treatment had a 0.52 RR (95% CI, 0.35-0.78).

Figure 2. Effect of Ramipril in Preventing Diabetes in Subgroups Defined at Randomization

Because ramipril reduced the risk of cardiovascular events and diabetic nephropathy, we assessed whether the higher occurrence of these clinical events in placebo-treated patients increased the likelihood of ascertainment of diabetes in this group. Similar stratified analyses by the occurrence of other outcomes was also examined. As noted in Table 2 the impact of ramipril on the development of diabetes could not be explained by any confounding factor such as preferential ascertainment in one group vs the other or use of concomitant medications.

Figure 2 demonstrates the results among subgroups of patients with different risk factors for developing diabetes. The results are consistent among those with a waist-to-hip ratio below or above the median of 0.93 and consistent among those with a body mass index (BMI) of 27.7 kg/m² or less or higher than 27.7 kg/m², those with or without a history or hypertension, those receiving or not receiving β-blockers or diuretics at randomization. A higher proportion of individuals without diabetes who were randomized to the placebo group than those randomized to the ramipril group received diuretics or β-blockers (drugs that are associated with glucose intolerance or diabetes) during the study. However, the RR for diabetes in the subgroup of individuals who never took these drugs during the study was consistent with the overall results (RR, 0.62; 95% CI, 0.43-0.90).

In 4074 patients weight was recorded at baseline and at study end. Weight increased by a mean (SD) of 0.98 (6.93) kg in the active group and 0.76 (8.10) kg in the control group.

COMMENT

These analyses indicate that ramipril reduces the risk of new diagnosis of diabetes among individuals with no previous history of diabetes. The magnitude of the benefit appears to be large and moreover, ACE-inhibitors also reduce macrovascular and microvascular complications of diabetes. Although the data on new diagnoses of diabetes were collected prospectively in the HOPE study, it was not a primary or secondary out-
come of the trial. Therefore the results should be interpreted with caution. Nevertheless, the results are plausible given the clear statistical significance and consistency of results across subgroups, as well as using a range of approaches to diagnosing diabetes.

The Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE) supports our findings that fasting glucose increased more with placebo (15.8 mg/dL [0.41 mmol/L]) than with ramipril (9.6 mg/dL [0.25 mmol/L]; P = .03). Among the patients with diabetes in the HOPE study, a significant reduction in HbA1c levels during serial annual recordings occurred during the first 2 years (absolute difference, 0.2%); In the UK Prospective Diabetes Study (UKPDS) and in the Captopril Prevention Project, patients randomized to receive ACE inhibitors had lower levels of HbA1c, or less development of diabetes compared with those taking β-blockers or diuretics. It is not clear whether the differences in development of diabetes observed in these studies are due to a protective effect of ACE inhibitors or an adverse effect of β-blockers or diuretics.

Hypokalemia substantially impairs the insulin secretory response to glucose, which may be favorably affected by ACE inhibitors. ACE inhibitors also lower aldosterone secretion and renal potassium wasting, which could preserve β-cell responsiveness. ACE inhibitors may increase islet blood flow and pancreatic β-cell perfusion by reducing angiotensin-2 mediated vasocostriction in the pancreas. These effects may potentially slow or reverse the decline in β-cell function.

ACE inhibitors may reduce insulin resistance in skeletal muscles, which increase insulin-mediated glucose disposal thereby decreasing the need for pancreatic insulin secretion. The increased insulin-mediated glucose uptake by skeletal muscle in response to an ACE inhibitor is due to increased bradykinin-mediated nitric oxide production and not to reductions in angiotensin 2 production or action. Several observations suggest that agents that increase nitric oxide (such as ACE-inhibitors) may also increase insulin-mediated glucose uptake. These observations include (1) both insulin-mediated vasodilation and skeletal muscle glucose metabolism are reduced in obese persons who do not have diabetes (ie, individuals at risk for diabetes) and in individuals with type 2 diabetes, (2) inhibition of nitric oxide production reproduces this effect in lean individuals, and (3) the effect on insulin sensitivity is greater than can be accounted for by just increased skeletal muscle blood flow. ACE inhibitors may also reduce insulin resistance at the liver and fat cell, which would reduce hepatic glucose production and lower free fatty acid levels.

Our data suggesting that ramipril, an ACE inhibitor, reduces the risk of developing diabetes mellitus require confirmation because of the enormous clinical and public health potential of these findings. We are therefore embarking on a large prospective trial (Diabetes Reduction Assessment with Ramipril and rosiglitazone Medication [DREAM]) among individuals with impaired glucose tolerance to evaluate prospectively whether ramipril prevents diabetes.

### Author Contributions


### Funding/Support

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### REFERENCES


