

Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy

Heart Outcomes Prevention Evaluation (HOPE) Study Investigators*

Summary

Background Diabetes mellitus is a strong risk factor for cardiovascular and renal disease. We investigated whether the angiotensin-converting-enzyme (ACE) inhibitor ramipril can lower these risks in patients with diabetes.

Methods 3577 people with diabetes included in the Heart Outcomes Prevention Evaluation study, aged 55 years or older, who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction, and who were not taking ACE inhibitors, were randomly assigned ramipril (10 mg/day) or placebo, and vitamin E or placebo, according to a two-by-two factorial design. The combined primary outcome was myocardial infarction, stroke, or cardiovascular death. Overt nephropathy was a main outcome in a substudy.

Findings The study was stopped 6 months early (after 4.5 years) by the independent data safety and monitoring board because of a consistent benefit of ramipril compared with placebo. Ramipril lowered the risk of the combined primary outcome by 25% (95% CI 12–36, $p=0.0004$), myocardial infarction by 22% (6–36), stroke by 33% (10–50), cardiovascular death by 37% (21–51), total mortality by 24% (8–37), revascularisation by 17% (2–30), and overt nephropathy by 24% (3–40, $p=0.027$). After adjustment for the changes in systolic (2.4 mm Hg) and diastolic (1.0 mm Hg) blood pressures, ramipril still lowered the risk of the combined primary outcome by 25% (12–36, $p=0.0004$).

Interpretation Ramipril was beneficial for cardiovascular events and overt nephropathy in people with diabetes. The cardiovascular benefit was greater than that attributable to the decrease in blood pressure. This treatment represents a vasculoprotective and renoprotective effect for people with diabetes.

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Introduction

People with diabetes mellitus are at high risk of cardiovascular disease. Epidemiological studies show that the risk of cardiovascular mortality is two to three times higher in men with diabetes and three to five times higher in women with diabetes than in people without diabetes.^{1–6} The age-adjusted prevalence of coronary heart disease in white adults who have diabetes is about 45%, compared with about 25% in individuals without diabetes,⁷ and cardiovascular disease accounts for about 70% of all deaths in people with diabetes mellitus.⁸

The presence of other risk factors increases the risk of cardiovascular disease in people with diabetes mellitus. The absolute annual risk of fatal and non-fatal cardiovascular disease in middle-aged and elderly people with type 2 diabetes is 4–5%.^{1,9–13} Despite decreases in the incidence of heart disease in the general population, the decline is much smaller in people with type 2 diabetes, and may even be rising in women with diabetes.¹³

Experimental studies, epidemiological studies, and clinical trials suggest that inhibitors of angiotensin-converting enzyme (ACE) may delay or prevent cardiovascular outcomes. For patients with diabetes, such benefit has been seen after acute myocardial infarction,¹⁴ in the presence of hypertension,^{15–19} and in the presence of a low ejection fraction or heart failure.²⁰ ACE inhibitors may also prevent overt nephropathy and other microvascular outcomes in patients with type 1 or type 2 diabetes.^{17,21,22}

Although studies suggest that ACE inhibitors may prevent or delay serious events in some subgroups, their role in a broader group of people with diabetes who are at high risk of cardiovascular events remains unknown. The Heart Outcomes Prevention Evaluation (HOPE) study investigated whether the addition of the ACE inhibitor ramipril to the current medical regimen of high-risk patients with diabetes mellitus can lower the risk of cardiovascular events. In the microalbuminuria, cardiovascular, and renal outcomes (MICRO) HOPE substudy, the effect of this intervention on the risk of overt nephropathy was investigated. We present here the results from these two studies for patients with diabetes mellitus.²²

Methods

Participants

The HOPE and MICRO-HOPE study protocol has been published.^{23,24} Briefly, people with and without diabetes were recruited, who were aged 55 years or older, and who had a history of cardiovascular disease (coronary artery disease, stroke, or peripheral vascular disease) or diabetes plus at least

| | Ramipril (n=1808) | Placebo (n=1769) |
|--|--------------------------|--------------------------|
| Demography | | |
| Mean age (years) | 65.3 (6.4) | 65.6 (6.6) |
| Female/male | 696 (38%)/ 1112 (62%) | 626 (35%)/ 1143 (65%) |
| Clinical characteristics | | |
| Mean (SD) body-mass index (kg/m ²) | 28.9 (4.8) | 28.6 (4.7) |
| Mean (SD) heart rate (beats/min) | 72.3 (11.4) | 72.5 (11.0) |
| Mean (SD) systolic blood pressure (mm Hg) | 141.7 (19.6) | 142.3 (19.5) |
| Mean (SD) diastolic blood pressure (mm Hg) | 80 (10.6) | 79.3 (10.7) |
| Mean (SD) ankle/arm systolic pressure (mm Hg) | 0.97 (0.19) | 0.96 (0.18) |
| Mean (SD) waist/hip ratio | 0.93 (0.09) | 0.93 (0.08) |
| Mean (SD) waist circumference (cm) | 99.9 (12.7) | 99.6 (12.4) |
| Microalbuminuria | 553 (31%) | 587 (33%) |
| Mean (SD) HbA _{1c} (%)* | 123 (30) | 124 (32) |
| Mean (SD) serum creatinine (μmol/L)* | 93.8 (22.3) | 94.0 (27.6) |
| Mean duration of diabetes (years) | 11.1 (10.2) | 11.8 (10.7) |
| Type 2 diabetes | 1774 (98%) | 1722 (97%) |
| History of hypertension | 1045 (58%) | 951 (54%) |
| Documented cholesterol >5.2 mmol/L | 1174 (65%) | 1161 (66%) |
| Current smoker | 274 (15%) | 270 (15%) |
| Previous coronary artery disease | 1046 (58%) | 1093 (62%) |
| Previous stroke/endarterectomy | 124 (7%) | 150 (8%) |
| Previous peripheral vascular disease | 311 (17%) | 361 (20%) |
| No previous cardiovascular disease | 604 (33%) | 515 (29%) |
| Hyperglycaemic control | | |
| Dietary therapy alone | 331 (18%) | 300 (17%) |
| Insulin therapy alone | 432 (24%) | 482 (27%) |
| Oral agents alone | 957 (53%) | 895 (51%) |
| Insulin plus oral agents | 88 (5%) | 92 (5%) |
| Other drugs | | |
| Acetylsalicylic acid | 982 (54%) | 998 (56%) |
| Diuretics | 350 (19%) | 350 (20%) |
| β-blockers | 510 (28%) | 505 (29%) |
| Calcium-channel blockers | 776 (43%) | 801 (45%) |
| Hypolipidaemic drugs | 409 (23%) | 390 (22%) |

*Measured at local laboratories; HbA_{1c} is reported as percentage above upper limit of normal for local laboratory.

Table 1: Baseline characteristics of participants with diabetes

one other cardiovascular risk factor (total cholesterol >5.2 mmol/L, HDL cholesterol ≤0.9 mmol/L, hypertension, known microalbuminuria, or current smoking). Key exclusion criteria were dipstick-positive proteinuria or established diabetic nephropathy, other severe renal disease, hyperkalaemia, congestive heart failure, low ejection fraction (<0.4), uncontrolled hypertension, recent myocardial infarction or stroke (<4 weeks), and use of or hypersensitivity to vitamin E or ACE inhibitors.²³ The study was done in 19 countries in North and South America and in Europe. The HOPE study protocol was approved by each institution's review board or ethics committee, and all participants provided written, informed consent.

Eligible participants were included who completed a run-in period, during which they received 2.5 mg ramipril daily for 7–10 days, followed by matching placebo for 10–14 days, who were at least 80% compliant, tolerated the drug without side-effects, and maintained a serum creatinine concentration of 200 μmol/L or lower and potassium concentration of 5.5 mmol/L or lower.

Study design

The study had a two-by-two factorial design with randomisation of participants to 10 mg ramipril or placebo taken once daily in the evening and 400 IU vitamin E or placebo daily. Follow-up visits were at 1 month and then every 6 months.

The combined primary endpoint was the development of myocardial infarction, stroke, or cardiovascular death. Secondary endpoints were total mortality, admission to hospital for congestive heart failure or unstable angina, cardiovascular revascularisation, or development of overt nephropathy. Other outcomes were any heart failure, worsening angina, and the development of diabetes in people with no history of the disorder. A preplanned analysis in the HOPE and MICRO-HOPE studies was to find out whether ramipril delayed or

| | Ramipril (n=1808) | Placebo (n=1769) |
|-----------------------------------|----------------------|---------------------|
| Stopped drug at any time | | |
| | 671 (37%) | 653 (37%) |
| Stopped drug by last visit | | |
| | 602 (33%) | 593 (34%) |
| Reasons for stopping* | | |
| Cough | 133 (7%) | 37 (2%) |
| Hypotension/dizziness | 30 (2%) | 24 (1%) |
| Angioedema | 5 (0.3%) | 1 (0.1%) |
| Hypertension | 60 (3%) | 100 (6%) |
| Clinical event | 138 (8%) | 171 (10%) |
| Other | 511 (28%) | 503 (28%) |
| ACE-inhibitor use | | |
| Non-study use at any time* | | |
| | 366 (20%) | 431 (24%) |
| Reasons for use | | |
| Heart failure | 116 (6%) | 133 (8%) |
| Proteinuria | 57 (3%) | 54 (3%) |
| Hypertension | 123 (7%) | 173 (10%) |
| Other | 181 (10%) | 191 (11%) |

*Categories not mutually exclusive.

Table 2: Reasons for stopping treatment

prevented these outcomes, as well as microalbuminuria or overt nephropathy, in participants with diabetes.^{22,25} All primary and secondary outcomes were documented on separate forms and centrally assessed by the event committee (who were unaware of the participants' assigned treatments) according to standard definitions.²³

Diabetes status and other demographic and clinical variables were established by history and physical examination at each visit. Participants were judged to have type 2 diabetes if they developed diabetes at age 30 years or older or were not taking insulin. We defined a history of hypertension as the taking of drugs to treat hypertension or blood pressure at recruitment higher than 160 mm Hg systolic or 90 mm Hg diastolic. Glycated haemoglobin (HbA_{1c}) and serum creatinine were assayed for participants with a history of diabetes in each study centre's local laboratory. Results for HbA_{1c} were expressed as the percentage higher than the upper limit of normal for the assay used. Any admissions for hypoglycaemia were recorded.

As part of the MICRO-HOPE substudy, urinary albumin excretion was measured at baseline, 1 year, and study end (4.5 years) by measuring the albumin/creatinine ratio in a first morning urine sample. Urine was stored at -70°C. The albumin/creatinine ratio was measured in four different laboratories during the study (in Canada, UK, Argentina, and Brazil) by different assay systems.²² Microalbuminuria was defined in 1993 as a ratio of 2 mg/mmol or higher in men and women.²²

Participants whose albumin/creatinine ratio was higher than 36 mg/mmol after randomisation were asked to provide a 24 h urine sample that was assayed in their local laboratory for total protein or urinary albumin; assays were chosen according to availability at each clinical site. Overt nephropathy was diagnosed if the 24 h urine albumin was 300 mg or more per day, if the 24 h urine total protein excretion was 500 mg or more per day, or if the measured albumin/creatinine ratio was higher than 36 mg/mmol and no 24 h urine result was available (ie, if there was evidence of clinical proteinuria). The measurements of actual daily excretion of albumin or protein for all 24 h urine collections were sent to the project office and all cases of overt nephropathy were centrally assessed.

Statistical analysis

The HOPE study was designed to recruit up to 4000 participants with diabetes. With the assumption of a constant event rate in participants with diabetes of 5% per year, this sample size would provide 90% power (two-sided α=0.05) to detect an 18% relative risk reduction in the rate of myocardial infarction, stroke, or cardiovascular death during the planned mean follow-up period of 5 years. The study was ended 6 months early on the recommendation of the independent data safety and monitoring board. Therefore, we report results for a median follow-up period of 4.5 years.

| Outcome | Ramipril (n=1808) | Placebo (n=1769) | Relative risk reduction (95% CI) | p |
|---|-------------------|------------------|----------------------------------|--------|
| Primary outcome | | | | |
| Combined | 277 (15.3%) | 351 (19.8%) | 25% (12 to 36) | 0.0004 |
| Myocardial infarction | 185 (10.2%) | 229 (12.9%) | 22% (6 to 36) | 0.01 |
| Stroke | 76 (4.2%) | 108 (6.1%) | 33% (10 to 50) | 0.0074 |
| Cardiovascular death | 112 (6.2%) | 172 (9.7%) | 37% (21 to 51) | 0.0001 |
| Secondary outcomes | | | | |
| Total mortality | 196 (10.8%) | 248 (14.0%) | 24% (8 to 37) | 0.004 |
| Unstable angina* | 213 (11.8%) | 207 (11.7%) | 0 (-21 to 17) | 0.99 |
| Heart failure* | 81 (4.5%) | 79 (4.5%) | 1% (-34 to 28) | 0.93 |
| Revascularisation | 254 (14.0%) | 291 (16.4%) | 17% (2 to 30) | 0.031 |
| Overt nephropathy† | 117 (6.5%) | 149 (8.4%) | 24% (3 to 40) | 0.027 |
| Other outcomes | | | | |
| Any heart failure | 198 (11.0%) | 236 (13.3%) | 20% (4 to 34) | 0.019 |
| Transient ischaemic attacks | 80 (4.4%) | 104 (5.9%) | 26% (1 to 45) | 0.04 |
| Worsening angina | 363 (20.1%) | 397 (22.4%) | 13% (0 to 24) | 0.057 |
| Laser therapy‡ | 170 (9.4%) | 186 (10.5%) | 22% (-9 to 28) | 0.24 |
| Dialysis | 10 (0.5%) | 8 (0.5%) | -20% (-205 to 53) | 0.70 |
| Overt nephropathy, † laser therapy, or dialysis | 273 (15.1%) | 312 (17.6%) | 16% (1 to 29) | 0.036 |

*Requiring admission. †Based on positive 24 h urine collection or albumin/creatinine ratio ≥ 36 mg/mmol if no 24 h urine available. ‡Laser therapy for retinopathy.

Table 3: Clinical outcomes for ramipril and placebo groups

We report only analyses done by intention to treat. Analyses were stratified according to randomisation to vitamin E or placebo by Cox's regression, to account for the factorial design. Results are reported as the relative risk reduction (95% CI), defined as 1 minus the relative hazard. Kaplan-Meier curves were used to estimate survival and were compared by log-rank test. Changes in continuous variables (ie, HbA_{1c}, albumin/creatinine ratio, blood pressure, serum creatinine) from baseline values, by treatment group, were analysed by ANOVA, adjusted for the baseline value. Albumin/creatinine ratios were transformed to account for non-normality and values were adjusted for the laboratories in which ratios were measured. Statistical tests for interaction were done with Cox's regression to assess the effect on the primary outcome of diabetes type, diabetes treatment, history of previous cardiovascular events, and presence of microalbuminuria or a history of hypertension at randomisation, and a similar approach was used to assess the effect of the presence of baseline microalbuminuria on the

development of overt nephropathy. Cox's regression models were also used to assess the effect of randomisation to ramipril on the primary outcome after adjustment for the change in blood pressure during the course of the study.

Results

Of all 9541 participants in the HOPE study, 3654 (39.3%) had diabetes at randomisation. 77 people who participated in another substudy in which they received only 2.5 mg ramipril or placebo were excluded from the analysis. Therefore, 3577 people with diabetes were included. The mean age was 65.4 years, 1322 (37%) were women, and 1996 (56%) had a history of hypertension. Baseline characteristics of participants in the ramipril and placebo groups were similar (table 1).

Of surviving participants at 1 year, 1486 (84%) patients in the ramipril group and 1516 (88%) in the placebo group were still taking study drugs, as were 1045 (65%) and 992 (66%), respectively, at the end of the study. At 4 years, 184 (12%) participants initially assigned ramipril and 220 (15%) initially assigned placebo were taking open-label ACE inhibitors. Non-medical reasons for stopping the study drug are shown in table 2. The only notable side-effect that led to excess discontinuation of study drug was cough, which was 5% more frequent among participants taking ramipril than among those taking placebo. The rate of admission to hospital because of hypoglycaemia did not differ between the ramipril and placebo groups (2 vs 2%), nor did the mean change in serum creatinine concentration.

The rate of the combined primary outcome of myocardial infarction, stroke, or cardiovascular death was significantly lower in the ramipril group than in the placebo group (relative risk reduction 25% [95% CI 12-36], $p=0.0004$). When the outcome components were analysed separately, the rates were also lowered significantly in the ramipril group, as were the secondary

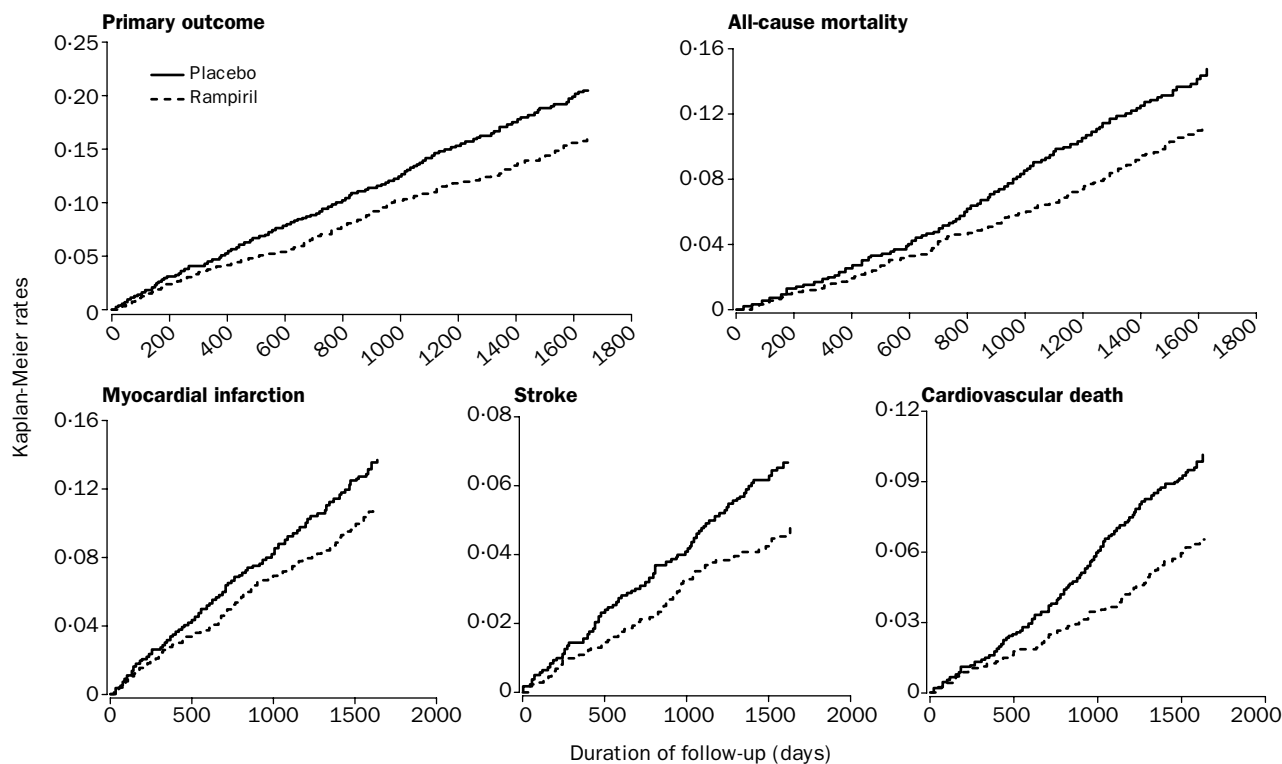


Figure 1: Kaplan-Meier survival curves for participants with diabetes

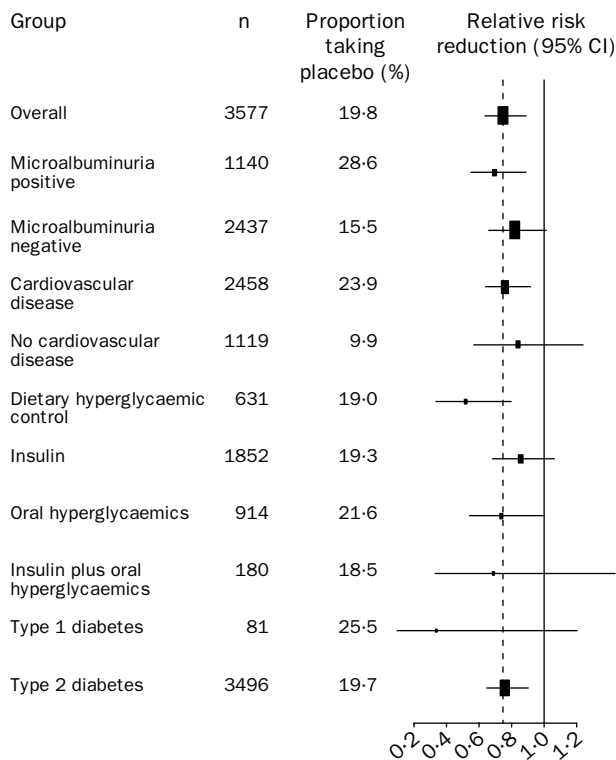


Figure 2: Effect of ramipril on combined primary outcome in subgroups

Size of symbol is proportional to number of participants in subgroup; broken line=overall relative risk.

outcomes (table 3, figure 1). Ramipril lowered the risk of the primary outcome by 16% (−14 to 39, $p=0.26$) after 1 year, and significantly by 26% (6–41, $p=0.011$) after 2 years. This effect was maintained at each subsequent year of follow-up.

Ramipril's benefit was noted irrespective of whether participants had a history of cardiovascular events (p for interaction=0.91), hypertension (p for interaction=0.93), or microalbuminuria (p for interaction=0.34), whether or not participants had type 1 or type 2 diabetes (p for interaction=0.32), and irrespective of current treatment for hyperglycaemia (p for interaction=0.51). The effect of ramipril in different diabetes-related subgroups is shown in figure 2.

Compared with baseline, mean absolute HbA_{1c} values increased by absolute amounts of 1.5% higher than the upper limit of normal in the ramipril group and 3.4% in the placebo group at 1 year ($p=0.04$). They fell by 0.1% among participants taking ramipril and rose by 2.2% among participants taking placebo at 2 years ($p=0.016$); the change from baseline in HbA_{1c} was the same for both groups at subsequent visits and at the end of the study (2.2% for ramipril and 2.0% for placebo respectively; $p=0.8$).

| Blood pressure (mm Hg) | Baseline | Change at 1 month | Change at 2 years | Change at final visit |
|------------------------|----------|-------------------|-------------------|-----------------------|
| Systolic | | | | |
| Ramipril | 141.7 | −5.3 | −2.7 | −1.9 |
| Placebo | 142.3 | −1.3* | 0.6* | 0.55† |
| Diastolic | | | | |
| Ramipril | 80.0 | −2.6 | −2.6 | −3.3 |
| Placebo | 79.3 | −0.3* | −1.05* | −2.3‡ |

* $p=0.0001$. † $p=0.0002$. ‡ $p=0.008$. p values for difference in change from baseline (ramipril vs placebo).

Table 4: Change in blood pressure with ramipril and placebo

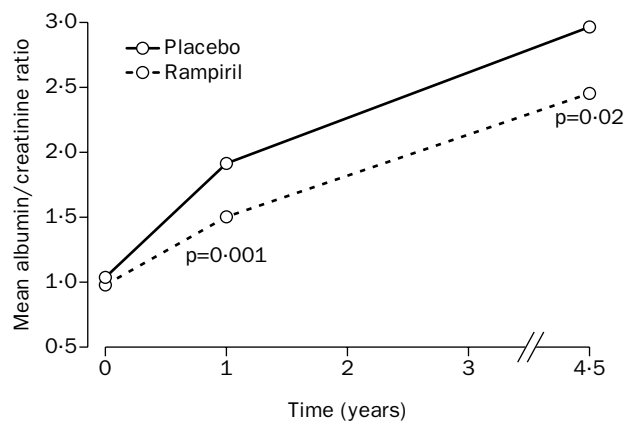


Figure 3: Effect of ramipril on degree of albuminuria

Geometric mean albumin/creatinine ratio of all participants with available 24 h urine collection is shown. Adjusted for laboratory in which assays done.

Blood pressure decreased slightly more among participants on ramipril than among those on placebo. By the end of the study, systolic blood pressure had fallen by 1.92 mm Hg and risen by 0.55 mm Hg in participants on ramipril and placebo, respectively ($p=0.0002$); diastolic blood pressure had fallen by 3.30 mm Hg and 2.30 mm Hg in the ramipril and placebo groups ($p=0.008$; table 4). After adjustment for changes in blood pressure, ramipril had the same effect on the primary outcome as that before adjustment (relative risk reduction 25% [12–36], $p=0.0004$).

Albumin/creatinine ratio was measured in 3498 (98%) participants at baseline, 2914 (83%) of 3511 at 1 year, and 2671 (86%) of 3106 at the end of the study. During follow-up, 345 (10%) participants developed an albumin/creatinine ratio of more than 36 mg/mmol and were asked to provide a 24 h urine collection to test for overt nephropathy. Results were available for 295 (85.5%) individuals. 117 (7%) participants on ramipril and 149 (8%) on placebo developed overt nephropathy (24% [3–40], $p=0.027$). When a more stringent definition of overt nephropathy was used and the analysis was restricted to people in whom 24 h urine results were available, 100 (6%) participants in the ramipril group and 124 (7%) in the placebo group were affected (22% [−2 to 40], $p=0.07$). Restriction of the definition of overt nephropathy even further to include only people who had a positive 24 h urine collection and who reported a history of laser therapy for retinopathy gave similar results (25% [−39 to 59], $p=0.36$).

225 (20%) participants with and 41 (2%) without baseline microalbuminuria developed overt nephropathy (relative risk 14.0 [10–19], $p<0.0001$). Ramipril lowered the risk of overt nephropathy in participants who did and did not have baseline microalbuminuria (p for interaction 0.51). Moreover, ramipril treatment led to a lower albumin/creatinine ratio than placebo at 1 year and at the end of the study end (figure 3). In participants without baseline microalbuminuria, the risk of new microalbuminuria was non-significantly reduced (relative risk reduction 9% [−4 to 20], $p=0.17$).

The effect of ramipril on a reported history of new laser therapy for diabetic retinopathy, and on a reported history of renal dialysis are shown in table 3. Ramipril reduced the risk of a combined microvascular outcome of overt nephropathy, dialysis, or laser therapy by 16% (1–29, $p=0.036$).

Discussion

Ramipril significantly lowered the risk of major cardiovascular outcomes by 25–30% in a broad range of high-risk middle-aged and elderly people with diabetes mellitus. The benefit was apparent irrespective of whether participants had a history of cardiovascular events, hypertension, or microalbuminuria, were taking insulin or oral antihyperglycaemic agents, or had type 1 or type 2 diabetes mellitus. The study had, however, low power to detect different effects in the subgroups. Since adherence to ramipril was 65% at the last visit, our results may underestimate the benefit that would have been seen with higher adherence.

Ramipril also lowered the risk of overt nephropathy, renal failure, or laser therapy. It had no long-term effect on glycaemic control.

When the major cardiovascular and microvascular events are taken into account, 15 high-risk people with diabetes would have to be treated with ramipril for a median of 4.5 years to prevent one individual from having a myocardial infarction, stroke, cardiovascular death, admission to hospital for heart failure, a revascularisation procedure, development of overt nephropathy, laser therapy for retinopathy, or renal dialysis.

We assessed blood pressure by cuff pressures, which is the normal approach in clinical practice and large randomised trials. We did not monitor ambulatory blood pressure and, therefore, excess overnight hypertension in the placebo group cannot be excluded. The risk reduction for cardiovascular events was, however, greater than would be expected from the observed mean difference in blood pressure between groups, which supports the results of the regression model showing that the effect of ramipril was much greater than can be attributed to its effect on blood pressure. For example, in the UK Prospective Diabetes Study (UKPDS),¹⁶ mean differences between groups in systolic and diastolic blood pressures of 10 mm Hg and 5 mm Hg, respectively, lowered the risk of myocardial infarction by 21% and stroke by 44%. Similarly, in participants with diabetes in the Systolic Hypertension in the Elderly (SHEP) study,²⁶ a decrease in systolic and diastolic pressures of 10 mm Hg and 2 mm Hg, respectively (using a diuretic-based approach), reduced the risk of cardiovascular events by up to 34%. By contrast, in the HOPE study the differences in systolic and diastolic blood pressures were only slight at 2.2 mm Hg and 1.4 mm Hg, yet the decreases in risk of myocardial infarction and stroke were similar to those seen in UKPDS.

These considerations suggest that the observed benefits of ramipril may be due largely to a protective effect of ACE inhibitors on the arterial wall.²⁷ Angiotensin II is a powerful direct vasoconstrictor, and promotes vascular smooth-muscle growth, possibly by inducing various proto-oncogenes and growth factors. It may also promote plaque rupture, possibly by stimulating release of endothelin, inhibiting fibrinolysis, and promoting thrombosis.²⁷ Bradykinin is a direct vasodilator and also promotes release of the vasodilating substances nitric oxide and prostacyclin. The effect of ACE inhibitors may, therefore, be mediated by the lowering of angiotensin-II concentrations and the increasing of bradykinin concentrations.

The observed effect of ramipril on cardiovascular outcomes are consistent with the results of other trials of

ACE inhibitors in people with diabetes that were designed as trials of lowering blood pressure. For example, the Captopril Prevention Project¹⁵ randomised 717 participants with diabetes mellitus who had severe hypertension in an open trial. After 6.1 years of follow-up those taking captopril had a 14% (95% CI 1–26) lower rate of myocardial infarction, stroke, or cardiovascular death than those taking diuretics and β -blockers.¹⁵ Similarly, the UKPDS study showed that the lowering of blood pressure with captopril or atenolol clearly decreased the risk of cardiovascular and microvascular events, but found no benefit of captopril over atenolol.¹⁷ Because 758 participants were randomly assigned captopril or atenolol and the event rate was 34%, the study had high power (about 80%) to detect large differences (eg, 30% differences in relative risk). However, differences in benefit between two active therapies are likely to be smaller than those between active treatments and placebo, and may typically be about 10%. Such differences could, therefore, have been missed. The results of other trials have supported a beneficial cardiovascular effect of ACE inhibitors over calcium-channel blockers, although this was not the primary aim of these studies.^{18,19,28}

For microvascular outcomes, our results are consistent with previous observations in individuals with type 1 and type 2 diabetes that ACE inhibitors lower the risk of diabetic nephropathy^{29,30} and renal failure,³¹ and are consistent with previous reports suggesting that ACE inhibition with lisinopril reduces the risk of diabetic retinopathy in normotensive people with type 1 diabetes.²¹ The findings are limited by the fact that the albumin/creatinine ratio was measured in four different laboratories, and that 24 h urine collections to confirm the presence of overt nephropathy were done in many different laboratories. Nevertheless, we adjusted analysis of the albumin/creatinine ratio for the laboratory in which it was measured and all 24 h urine results were adjudicated centrally. Moreover, a beneficial effect of ramipril was seen despite the increased variability because of the different laboratories, which would lead to an underestimate of the effect of ramipril on overt nephropathy.

The results are also limited by the fact that overt nephropathy was not confirmed by a renal biopsy—a point that may be important because of observations of a high rate of non-diabetic renal disease in people with type 2 diabetes.^{32,33} Nevertheless, a report and review of morphological data from several studies suggests that clinical proteinuria is a reliable marker for overt diabetic nephropathy in people with type 2 diabetes.³⁴ Moreover, our results were unchanged after use of a more stringent definition for diabetic nephropathy (a positive 24 h urine collection plus a history of retinopathy that was treated with laser therapy). In addition, epidemiological studies show a high rate of renal failure in people with type 2 diabetes and overt nephropathy defined on the basis of clinical proteinuria alone.³³ For retinopathy alone, these results are clearly limited by the fact that retinal photographs were not taken. Nevertheless, a history of laser therapy for diabetic retinopathy is likely to be highly specific, but not sensitive, for serious diabetic retinopathy.

Because the HOPE study was not designed to be a trial of the effect of lowering blood pressure, only general comparisons can be made with other studies. In the HOPE study, ramipril was added to participants' current

treatments at randomisation and was not titrated to achieve prespecified blood pressures. Therefore, ACE inhibition with ramipril is most appropriately viewed for this study as a preventive intervention with multiple mechanisms of benefit, including lowering of blood pressure. Its addition to other proven prevention strategies such as decreasing blood pressure, glycaemic control, lipid lowering, stopping smoking, and aspirin should further lower the risk of cardiovascular and microvascular events in people with diabetes.

HOPE study organisation

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