The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: results from the PERSUADE substudy

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Aims The aim of this study was to assess the effect of the angiotensin converting enzyme inhibitor perindopril on cardiovascular events in diabetic patients with coronary artery disease.

Methods and results A total of 1502 diabetic patients with known coronary artery disease and without heart failure of 12,218 overall in the EUROPA trial on Reduction Of cardiac events with Perindopril in stable coronary Artery (EUROPA) disease were randomized in a double-blinded manner to perindopril 8 mg once daily or placebo. Follow-up was for a median of 4.3 years. The primary end point was cardiovascular death, non-fatal myocardial infarction, and resuscitated cardiac arrest. Perindopril treatment was associated with a non-significant reduction in the primary endpoint in the diabetic population, 12.6% vs. 15.5%, relative risk reduction 19% ([95% CI, −7 to 38%], P = 0.13). This was of similar relative magnitude to the 20% risk reduction observed in the main EUROPA population.

Conclusion Perindopril tends to reduce major cardiovascular events in diabetic patients with coronary disease in addition to other preventive treatments and the trend towards reduction was of a similar relative magnitude to that observed the general population with coronary artery disease.

**KEYWORDS**
Randomized controlled trial; ACE inhibitor; Diabetes mellitus; Stable coronary disease; Secondary prevention

**Introduction**

The initial successes of angiotensin converting enzyme (ACE) inhibition in the secondary prevention of myocardial infarction (MI) and heart failure1–6 have led to investigation of an expanded role for their use in cardiovascular disease. Post-hoc and subgroup analysis of the earlier trials of ACE inhibitors indicate a substantial benefit of treatment with ACE inhibition in diabetic patients post-MI,7 and in heart failure.8 In addition to well-established benefits associated with the use of ACE inhibitors in patients with heart failure and ventricular dysfunction, the Heart Outcomes Prevention Evaluation (HOPE) study showed a 22% relative risk reduction in cardiovascular events in patients aged 55 years and over at high risk of cardiovascular events. In particular, the MICRO-HOPE study showed a 25% relative risk reduction in primary outcome in diabetics, the majority of whom had pre-existing cardiovascular disease.9 The cardiovascular benefits of ACE inhibition have more recently been extended to encompass a broader range of baseline risk. The EUROPE trial on Reduction Of cardiac events with Perindopril in stable coronary Artery (EUROPA) study, a 12,182 patient, prospective, double-blind randomized controlled trial over 4 years, in established coronary artery disease without known heart failure, indicated that treatment with perindopril 8 mg once daily was associated with a 20% relative risk reduction (P = 0.0003) in the primary endpoint (cardiovascular death, MI, and cardiac arrest) in all patients with stable coronary disease.10

Cardiovascular disease is the leading cause of death and morbidity in the diabetic population.12,13 Quite apart from the fact that diabetes places an individual at higher risk than the general population of developing coronary and other cardiovascular disease,12,13 the presence of diabetes in the context of established disease portends a worse clinical outcome. Diabetes in patients with coronary disease is associated with approximately double the rate of major cardiovascular events observed in the non-diabetic population.14 The effects of ACE inhibition in diabetic patients are of particular interest, given the higher prevalence and greater risk associated with cardiovascular disease in the context of diabetes, and potential additional benefits on renal function and progression of diabetes. Although studies suggest that ACE inhibitors may prevent cardiovascular events in some diabetic patients, their role in diabetic coronary patients remains unknown. The PERindopril Substudy in Coronary Artery Disease and DiabEtes (PERSUADE) study, the diabetic substudy

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of EUROPA was planned to investigate the effect of the ACE inhibitor perindopril in reducing cardiovascular death, MI, and other cardiovascular outcomes in diabetic patients with stable coronary disease without heart failure.

**Methods**

The EUROPA study was a large double blindered, randomized placebo controlled study which assessed the effect of perindopril 8 mg once daily on outcome in a stable coronary disease population. The main outcome, the design, organization, cardiovascular endpoint definitions, exclusion criteria, and baseline characteristics of the EUROPA trial\(^1\) have previously been published, but are outlined again briefly.

**Population**

Men and women >18 years of age, with objective evidence of coronary disease, but without clinical heart failure were enrolled in the study. Previous MI, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or angiographically documented coronary stenosis >70% were accepted as objective evidence of coronary disease or a positive stress test in symptomatic males. The main exclusion criteria were clinical evidence of heart failure, planned revascularization, hypotension (sitting systolic blood pressure of <110 mmHg) or uncontrolled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure of >100 mmHg), recent (<1 month) use of ACE inhibitor or angiotensin receptor blockers therapy, and renal insufficiency (creatinine >150 \(\mu\)mol/L) or serum potassium >5.5 mmol/L. Each institution’s review board or ethics committee reviewed the protocol and all participants provided informed consent. Of the 12,218 patients randomized in EUROPA, 1502 (12%) had an established diagnosis of diabetes at baseline, based on self-report of physician diagnosis or patient records. These patients form the main population for analysis in the PERSUADE study. PERSUADE was a preplanned substudy of the EUROPA study. However, forced enrollment of diabetics to achieve a pre-specified target proportion of diabetic patients did not occur and the diabetic sample size was not determined prior to the study.

**Baseline measurements, randomization, and follow-up**

Enrolled patients received perindopril 4 mg (or 2 mg in the elderly) titrated up to a maximum of 8 mg once daily over a 4-week run-in period. Patients who completed this run-in period without clinically significant adverse effects were randomized to perindopril 8 mg or placebo. Patients were followed-up at 3, 6, and 12 months and every 6 months thereafter for a median of 4.3 years. Blood pressure was recorded twice in the sitting position using a standard sphygmomanometer after at least 5 min rest at each visit and sodium, potassium, and creatinine were measured during the run-in, at randomization and once yearly therefrom. Treatment for diabetes was at the discretion of the patient’s physician.

Patient recruitment and randomization was conducted from October 1997 to June 2000. The protocol was modified during the study to redefine the primary endpoint for the following reasons. First, the primary endpoint was defined as total mortality, non-fatal MI, and unstable angina. However, during the course of the study new methods of detection of myocardial injury/infarction were introduced into clinical practice, and new recommendations made jointly by the European Society of Cardiology (ESC) and American College of Cardiology (ACC) regarding definition of MI in 2000. These guidelines recommended that all patients with raised markers of myocardial necrosis (cardiac troponin T, I or CK-MB) should be labelled MI and distinguished from unstable angina without myocardial necrosis. Unstable angina without myocardial necrosis was no longer judged an appropriate endpoint given its subjective diagnosis. Secondly, the contribution of cardiovascular mortality to the overall mortality in the population was lower than expected, that is ~60%. As ACE inhibition was not expected to improve non-cardiovascular mortality, cardiovascular mortality was deemed more appropriate to include in the primary endpoint than total mortality. The primary endpoint was therefore redefined as cardiovascular death, non-fatal MI, or successfully resuscitated cardiac arrest in January 2002, more than a year before the trial was completed, with no knowledge of the trial outcome at the time. Power calculations using the new endpoint suggested that the duration of the trial should be extended by 1 year to accrue the required number of events. These modifications were agreed by the EUROPA steering committee.

Thus, for the final analysis, the primary endpoint was a composite outcome of cardiovascular mortality, non-fatal MI, or successfully resuscitated cardiac arrest. A diagnosis of MI was based on the recommendations of the ESC and ACC.\(^1\) Cardiovascular mortality was adjudicated by the central critical event committee on the basis of autopsy results if available or documentary evidence from medical records of the immediate clinical history prior to death. Other secondary endpoints included, individually and in various combinations, total mortality, revascularization, stroke, hospitalization for unstable angina, and hospitalization for heart failure. These endpoints were included in analysis only if confirmed by the independent critical event committee. Specific diabetes related endpoints included hospitalization for diabetes or peripheral vascular disease, doubling of serum creatinine, or rise in creatinine >170 \(\mu\)mol/L.

**Statistical analysis**

We used the log rank test in an intention to treat analysis for the time to first event for the primary and other secondary endpoints. The cumulative distribution of events over time was examined using the Kaplan–Meier method. Cox’s proportional-hazards model was used to measure treatment effect, by deriving relative risks and relative risk reductions \([1 − RR] \times 100\) with 95% confidence intervals, for the primary and secondary clinical endpoints analysed by time to first event. The proportional hazards assumption was not formally tested. Event rates presented were calculated using appropriate survival analysis techniques.

Tests of significance were two-sided and a significance level of \(P < 0.05\) was used. Adjustments were not made for multiple comparisons. Subsidiary comparisons included assessment of the effect of treatment with perindopril not just on first events but on first and subsequent (all) events during the scheduled treatment period. The mean difference in blood pressure over follow-up was calculated as an average of the mean difference between the treatment groups at each time point. Differences in blood pressure between treatment and placebo groups were compared over time using a repeated measures procedure (proc MIXED) in SAS v 8.02. Patients were used as a random factor in the analysis. Time was not included as a continuous variable in the mixed model, as visit was included. Treatment and interaction between visit and treatment were included. Differences between treatment and placebo groups in creatinine and change in creatinine from baseline, which was calculated at randomization and annually thereafter, were also assessed by this procedure.

**Role of the funding source**

Representatives of the sponsor were non-voting members of the study executive committee and were involved with the executive committee in the study design, interpretation of the data, the writing of the report, and the decision to submit the paper for publication. The sponsor was not involved in the data collection and data analysis.

**Results**

Between October 1997 and June 2000, 1502 patients with diabetes and coronary disease were randomized to
perindopril or placebo, along with 10,716 who did not have a diagnosis of diabetes at baseline (Figure 1). Of the patients with known diabetes, 18% were on insulin therapy at baseline. Baseline characteristics of the diabetic population are shown in Table 1, with those of the overall EUROPA population for comparison. The perindopril and placebo groups were evenly matched for baseline characteristics. The mean age of diabetic population was 62 years, with 18% female. A history of MI was present in 67%. Compared with the overall EUROPA population, the diabetic population had significantly higher prevalences of hypertension, and pre-existing non-coronary vascular disease, with 6% having had a previous transient ischaemic attack (TIA) or stroke, and 13% peripheral vascular disease. The use of secondary preventative medication was widespread in the diabetic population as in the EUROPA population and not significantly different between the perindopril and placebo groups (Table 2).

Severe or even moderate angina was rare with 70% of the population without any limitation of ordinary activity by angina [Canadian Cardiovascular Society (CCS) Class I]. Only 27% of the population had slight limitation of activity (CCS Class II) and only 3% had Class III symptoms or above. Patients with NYHA Class II symptoms or above, or signs of heart failure on examination were not included in the study. The frequency of use of open label ACE inhibitor therapy at any time during the study was significantly greater in the placebo group than in the perindopril treated group in patients known to have diabetes at baseline. Calcium channel blockers and diuretics were also used significantly more frequently in the placebo group (Table 2).

A primary endpoint, either cardiovascular mortality or MI or cardiac arrest occurred in 121 patients in the placebo group and 91 patients in the perindopril group, corresponding to a relative risk reduction of 19% (95% CI −7, 38) \( P = 0.131 \) (Table 3, Figure 2). This is comparable to a relative risk reduction of 19% (95% CI 18, 29) in primary endpoint with perindopril in patients without a diagnosis of diabetes at the outset of the study, or 20% (95% CI 9, 29) in the EUROPA study as a whole. The benefit is of the same relative magnitude to that reported in EUROPA but the absolute effect is greater because of the higher event rate in the diabetic population. The Kaplan–Meier curve indicates that the cumulative incidence of the primary endpoint in the perindopril group becomes less than that of the placebo group from about 3 years. From there the separation of the curves persists until the study end. The combined secondary endpoints comprised total mortality, MI, unstable angina, and cardiac arrest; and cardiovascular mortality, MI, and stroke are also reduced by a considerable, but non-statistically significant extent. Relative risk reductions are 15% (−5, 32%) and 14% (−11, 34), respectively (Table 3). Individual secondary endpoints are also reduced, albeit non-significantly, by perindopril (Figure 3). Although the 23% relative risk reduction in fatal and non-fatal MI failed to meet significance, the incidence of non Q-wave MI was lowered significantly by perindopril, relative risk reduction 34% (95% CI, 0.1–56%, \( P = 0.048 \)).

Effect relative to blood pressure and blood pressure lowering

During the run-in phase from screening to randomization, when all patients were taking perindopril, the mean ± SD drop in blood pressure was 7 ± 15/4 ± 9 mmHg (Figure 4). Following randomization, both systolic and diastolic blood pressure were significantly lower in the perindopril treated group when compared with the placebo group (\( P < 0.0001 \) in both cases). Treatment and visit were statistically significant in systolic and diastolic blood pressure analysis. The mean difference between the perindopril and placebo groups over the course of follow-up period was 4.6/1.8 mmHg. To evaluate the effect of perindopril on cardiovascular outcome relative to its hypotensive action, we examined the treatment effect for tertiles and quartiles of systolic and diastolic blood pressure before treatment (Figure 5 illustrates results when analysed by tertiles of blood pressure, analysis by quartiles did not alter the result). The observed effects of perindopril did not vary according to baseline systolic or diastolic pressure. We also determined the relative risk reduction for tertiles and quartiles of observed drop in systolic or diastolic blood pressure in response to treatment. Patients in the lowest tertiles (systolic and diastolic) of blood pressure reduction are those patients who displayed no reduction in blood pressure while on open label treatment during the run-in phase. Among these patients, the perindopril treated group had significantly lower systolic and diastolic blood pressures during the course of the study, but even in the perindopril treated arm, blood pressure was not reduced below baseline at any point. In these patients in the lowest tertiles of systolic and diastolic blood pressure reduction, treatment with perindopril substantially reduced the primary endpoint, relative risk reduction 46% (13, 67%), \( P = 0.011 \) and 34% (−13, 62%), \( P = 0.127 \) respectively (Figure 6).
Effect on serum creatinine

The mean serum creatinine levels at baseline and at randomization were 94 ± 18 and 95 ± 18 µmol/L, respectively. The mean change from baseline creatinine did not differ between the two treatment groups at any time point during the period of follow-up. Doubling of creatinine from baseline (at any time point during follow-up) occurred in ~1% of patients overall over the 4 year follow-up, and the onset of renal dysfunction, defined as a rise in serum creatinine above 170 µmol/L at any time point occurred in 1.6% of patients. There were no clinically or statistically significant differences between the treatment groups in either doubling of creatinine or onset of renal dysfunction or when both of these renal endpoints were combined. Peripheral vascular hospitalizations were also rare, occurring in only

Table 1  Baseline characteristics of patients with known diabetes at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PERSUADE overall</th>
<th>EUQUA overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Perindopril (n = 721)</td>
<td>Placebo (n = 781)</td>
</tr>
<tr>
<td>Mean ± SD age (years)</td>
<td>61.9 (± 8.5)</td>
<td>62 (± 8.5)</td>
</tr>
<tr>
<td>Female sex</td>
<td>124 (17.2)</td>
<td>147 (18.8)</td>
</tr>
<tr>
<td>Manifestations of coronary disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>470 (65.2)</td>
<td>530 (67.9)</td>
</tr>
<tr>
<td>PCI</td>
<td>194 (26.9)</td>
<td>199 (25.5)</td>
</tr>
<tr>
<td>CABG</td>
<td>217 (30.1)</td>
<td>260 (33.3)</td>
</tr>
<tr>
<td>Previous cardiovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous CHF</td>
<td>14 (1.9)</td>
<td>26 (3.3)</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>41 (5.7)</td>
<td>42 (5.4)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>97 (13.5)</td>
<td>93 (11.9)</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>276 (38.3)</td>
<td>317 (40.6)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>438 (60.7)</td>
<td>474 (60.7)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>85 (11.8)</td>
<td>95 (12.2)</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD weight (kg)</td>
<td>82.5 (± 13.3)</td>
<td>81.6 (± 12.9)</td>
</tr>
<tr>
<td>Mean ± SD systolic BP (mmHg)</td>
<td>139.8 (± 15.4)</td>
<td>140.4 (± 15.7)</td>
</tr>
<tr>
<td>Mean ± SD diastolic BP (mmHg)</td>
<td>81.4 (± 8.2)</td>
<td>81.8 (± 8.4)</td>
</tr>
<tr>
<td>Mean ± SD heart rate (beats/min)</td>
<td>70 (± 10)</td>
<td>70.4 (± 10.7)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet inhibitors</td>
<td>665 (92.2)</td>
<td>725 (92.8)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>449 (62.3)</td>
<td>505 (64.7)</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>380 (52.7)</td>
<td>406 (52)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>268 (37.2)</td>
<td>297 (38)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>373 (51.7)</td>
<td>405 (51.9)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>88 (12.2)</td>
<td>104 (13.3)</td>
</tr>
</tbody>
</table>

Baseline characteristics [number of patients (%) or mean ± SD] at screening, concomitant medication at randomization. previous CHF: A history of congestive heart failure at any time in the past; hypertension: blood pressure over 160/95 mmHg or receiving antihypertensive treatment; hypercholesterolaemia: cholesterol > 6.5 mmol/L or on lipid lowering therapy.

Table 2  Frequency of use of cardiovascular medications in patients with known diabetes either at baseline, or at the final visit, or at any point during the study

<table>
<thead>
<tr>
<th></th>
<th>Baseline (%)</th>
<th>Final visit (%)</th>
<th>At any time during study (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Perindopril</td>
<td>Placebo</td>
<td>Perindopril</td>
</tr>
<tr>
<td>Platelet inhibitors</td>
<td>92</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>62</td>
<td>65</td>
<td>62</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>53</td>
<td>52</td>
<td>67</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>37</td>
<td>38</td>
<td>34b</td>
</tr>
<tr>
<td>Nitrates</td>
<td>52</td>
<td>52</td>
<td>42</td>
</tr>
<tr>
<td>Diuretics (non-potassium sparing)</td>
<td>11</td>
<td>11</td>
<td>18b</td>
</tr>
<tr>
<td>Open label ACE inhibitors</td>
<td>0</td>
<td>0</td>
<td>7.1</td>
</tr>
<tr>
<td>Angiotensin blockers</td>
<td>0</td>
<td>0</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*aNo significant differences in any concomitant medication between perindopril and placebo treated groups at baseline.

*bStatistically significant differences between placebo and perindopril treated groups.
1% of the population during the study, and rates were not significantly affected by treatment.

**Discussion**

Our findings suggest that diabetic patients with stable coronary disease without heart failure obtain similar relative benefits in terms of reduced cardiovascular events from treatment with perindopril to the general coronary disease population. Although not statistically significant, the 19% relative risk reduction ($P = 0.13$) in the primary endpoint closely matches the 20% relative risk reduction ($P = 0.0003$) in the main EUROPA population, as do the 23 and 46% relative risk reductions observed for MI and hospitalization for heart failure, respectively. The results indicate a consistent trend towards benefit in the perindopril treated group across secondary endpoints tested and a significant reduction in non-Q-wave MI. But the results are not just internally consistent. The 23% relative risk reduction in MI is comparable to the 20% reduction in this endpoint in the HOPE population or the 22%

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**Table 3** Effect of treatment with perindopril on primary and secondary endpoints in patients with known diabetes at baseline

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Perindopril ($n = 721$)</th>
<th>Placebo ($n = 781$)</th>
<th>Relative risk reduction (%)</th>
<th>[95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Event rate$^a$ (%)</td>
<td>Events per 1000 patient years</td>
<td>n</td>
<td>Event rate$^a$ (%)</td>
<td>Events per 1000 patient years</td>
</tr>
<tr>
<td>Cardiovascular mortality, MI, and cardiac arrest</td>
<td>91</td>
<td>13.1</td>
<td>32.3</td>
<td>121</td>
<td>17.9</td>
</tr>
<tr>
<td>Total mortality, non-fatal MI, unstable angina, and cardiac arrest</td>
<td>148</td>
<td>21.0</td>
<td>54.4</td>
<td>188</td>
<td>28.0</td>
</tr>
<tr>
<td>Cardiovascular mortality, MI, and stroke</td>
<td>103</td>
<td>14.7</td>
<td>36.9</td>
<td>130</td>
<td>19.2</td>
</tr>
</tbody>
</table>

$^a$Event rate calculated using survival analysis technique.

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**Cumulative frequency of primary endpoint**

![Image of Kaplan-Meier curves indicating the cumulative incidence of the primary endpoint, cardiovascular death, MI, and cardiac arrest in the diabetic population.](image-url)

Figure 2: Kaplan-Meier curves indicating the cumulative incidence of the primary endpoint, cardiovascular death, MI, and cardiac arrest in the diabetic population.
reduction observed in the diabetic substudy of HOPE, and similar in magnitude to the 21–23% relative risk reduction in MI in the SOLVD trials and in a meta-analysis of trials of ACE inhibitors.4,5,2 Although the GISSI-3 trial indicated that the relative risk reduction in cardiovascular death associated with early administration of lisinopril post-MI was significantly greater in the diabetic group compared with the non-diabetics, this is not a universal finding.16

In fact, in the TRACE7 and SOLVD trials, there was no interaction between diabetic status and drug assignment with regard to any of the major endpoints when this was formally assessed.8 In addition, although PERSUADE was a prespecified substudy of EUROPA, it was not powered to show statistical significance having only 47% power to detect the observed differences in primary endpoint between the treatment groups.
The high rate of events in the diabetic population, approaching double that in the overall population or those without a diagnosis of diabetes at baseline, means that a relative risk reduction in this population of similar magnitude to that in the overall population is associated with greater absolute risk reduction. Considering that the use of secondary prevention, platelet inhibitors, statins, and beta blockers is so widespread, greater than used in HOPE or observed in large surveys of clinical practice in Europe, the additional benefit of ACE inhibitor therapy might be expected to be attenuated, yet the relative magnitude of the effect was maintained. Tight control of blood pressure has been proven to reduce macrovascular complications of diabetes and improve cardiovascular outcome in hypertensive diabetic patients. Tight control of blood pressure may be more important in the diabetic population than in non-diabetics. Targeted multifactorial intervention programmes including intensive blood pressure lowering and the use of ACE inhibition irrespective of blood pressure, have also been shown to be effective in reducing cardiovascular events in diabetic patients.

It has been discussed if it is the ACE-inhibition per se or the concomitant blood pressure reduction which relates to the beneficial effects of ACE inhibitors on cardiovascular outcome. The reduction in blood pressure achieved with perindopril treatment during the course of this study (4.6/1.8 mmHg) is within the range (3–6 mmHg systolic/1–4 mmHg diastolic) observed in other previous trials of placebo controlled trials of ACE inhibitor therapy (HOPE, PART2, QUIET, and SCAT). Meta-analysis of the results of these trials has not indicated any heterogeneity in the effects of ACE inhibitors in terms of cardiovascular outcomes at this level of blood pressure reduction. Although there are methodological limitations to the analysis, no direct evidence to suggest that higher levels of baseline systolic or diastolic blood pressure, or a greater fall in blood pressure with treatment favourably influenced the effect of treatment with perindopril was observed. This is consistent with the results of the metaanalysis of cardiovascular protection and blood pressure reduction by Staessen et al. which indicated that blood pressure at baseline contributed less to variance in outcome than blood pressure differences during follow-up. However, it is noteworthy that in the PERSUADE population the benefit of treatment was significant in the lowest tertile of initial reduction in systolic blood pressure, mostly composed of patients who had no fall in blood pressure, maintained over the course of the study in the perindopril group. Although it is not possible to conclude that the blood pressure lowering effect did not play a role in the treatment benefit observed, this finding supports the concept of pleiotropic vasculoprotective effects of ACE inhibition in addition to the blood pressure lowering effects.

There are several putative mechanisms by which ACE inhibition may delay progression of atherosclerosis and reduce cardiovascular events. First, ACE inhibition may retard the accelerated atherosclerotic progression typical of diabetes. Murine models using Apo-E deficient mice as experimental models of atherosclerosis have shown that induction of diabetes is associated with a four-fold increase in atherosclerotic plaque area over a 20 week period. Treatment with perindopril in the diabetic mice results in significantly less plaque development, similar to control animals. In addition to effects on plaque volume, plaque composition is also adversely affected by diabetes with increased macrophage infiltration of the plaque, which is ameliorated by perindopril treatment. Connective tissue growth factor and cellular adhesion molecules such as VCAM and ACE gene expression are all increased in diabetic atherosclerosis and reduced by perindopril. ACE inhibitors also exert a positive effect on the endothelial dysfunction, which is often a feature of coronary disease. Perindopril can acutely correct the endothelial dysfunction seen in hypertensive coronary arteries and at long-term increase coronary reserve and reduce myocardial vascular resistance. This effect may be caused indirectly by reduction in angiotensin II or an increase in bradykinin, which serve to inactivate and augment release of nitric oxide, respectively. A more recent discovery of increased constitutitive NO synthase expression in the coronary endothelium in response to perindopril suggest that there may also be a more direct effect on nitric oxide production. This in turn has other beneficial effects including a reduction in platelet adhesion and aggregation. Finally ACE inhibition may exert further antithrombotic effects by reducing angiotensin II, which exerts its prothrombotic effect by reducing platelet adhesion and aggregation. A more recent discovery of increased constitutitive NO synthase expression in the coronary endothelium in response to perindopril suggest that there may also be a more direct effect on nitric oxide production. This in turn has other beneficial effects including a reduction in platelet adhesion and aggregation. Finally ACE inhibition may exert further antithrombotic effects by reducing angiotensin II, which exerts its prothrombotic effect by increasing PAl-1 and fibrinogen.

In this group of diabetics with well-controlled blood pressure, the incidence of overt renal dysfunction or doubling of serum creatinine was rare. This is in keeping with previous findings indicating that, although diabetes is one of the most frequent causes of end stage renal disease, in fact cardiovascular events constitute a far greater morbidity burden and mortality risk to the type 2 diabetic population than renal disease. It is not surprising therefore that no significant treatment effect was observed when serum creatinine levels were used as the indicator of renal disease.

Limitations

The definition of diabetes at baseline was an established diagnosis of diabetes. Thus the true diabetic population is likely to have been larger, however without measurement of fasting glucose levels prior to inclusion in all patients, no conclusion may be drawn on this point. Requirement of insulin therapy was documented in all patients with diabetes at baseline. However, other forms of treatment for diabetes and pre-existing complications of diabetes

| SBP ≤ 132 mmHg | Placebo better |
| SBP > 132.5 and < 145 mmHg | |
| SBP > 145 mmHg | |
| DBP ≤ 79.5 mmHg | |
| DBP > 80 and < 84.5 mmHg | |
| DBP > 84.5 mmHg | |

Figure 5 Relative risk (95% CI) of primary endpoint associated with treatment with perindopril, in diabetic patients according to tertiles of systolic or diastolic blood pressure at baseline.
were documented in only 49% of patients with established diabetes at baseline, and the duration of the diagnosis was not recorded. Some 11% of the diabetic subpopulation declined to participate in the extended study duration. As the maximum benefit of perindopril in the diabetic populations would appear to have been after 3 years, the reduced numbers in the extended follow-up may have reduced the statistical significance of the effects of perindopril in the diabetic population which was already small. As bias may have been introduced in interpretation of the effect of treatment on blood pressure due to missing data, the levels of the blood pressures have been stable over a period of 4 years. In the last year, when most of the missingness occurs, there was minimal change in blood pressure with respect to the previous period. A possible introduction of bias would be from the patients who had died during follow-up and so did not have blood pressure recordings during the final year, however with such a low total mortality rate, this contributes a very small amount to the overall numbers included. It is unlikely that, given the stability of blood pressure over the preceding years, if the measurements had been available, that the observed pattern in blood pressure would have changed substantially. Even if there is a potential for bias, its size is far outside the range of clinical importance. Finally, definite conclusions as to the importance or lack of importance of baseline blood pressure in our analysis are limited by the fact that the overall results failed to meet statistical significance, and also this part of the analysis was performed as a post-hoc analysis.

Conclusions

The results of PERSUADE are consistent with previous reports of beneficial cardiovascular effects of ACE inhibitors in the diabetic population. A statistically significant result was not obtained but the study did not have sufficient power to detect significant differences between the perindopril and placebo treated groups. Because the cardiovascular event rate in diabetics is higher than the general population with coronary disease, any relative reduction in events will translate into a greater absolute reduction, but direct evidence of additional benefit for diabetic patients compared with the overall population with coronary disease in relative terms has not been proven. Finally, the trend towards a reduction in cardiovascular events in the diabetic population with coronary disease observed with perindopril treatment was despite excellent use of other secondary preventative therapy (93% on antiplatelet therapy, 64% on beta-blockers, and 52% on lipid-lowering therapy at baseline), and was of the same relative magnitude as in the overall study and previous trials.

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Appendix

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