Background
ACE inhibitors have a special role in diabetes care. They have been proven to reduce urinary albumin excretion and reduce the rate of progression of diabetic nephropathy and retinopathy. There is proven benefit post myocardial infarction, with a greater beneficial effect in patients with diabetes in comparison to those without. The effect of ACE inhibitors in patients who have low ejection fractions or overt cardiac failure is well described. More recent studies indicate other benefits of ACE inhibitors such as improving dyslipidaemia and insulin sensitivity.

Cardiovascular disease is the commonest cause of mortality among patients with type 2 diabetes. A recent study reports the standardised mortality ratio to be considerably higher in people with diabetes with the vast majority of the excess due to cardiovascular disease (type 1 diabetes: women x 6.41, men x 2.94, type 2 diabetes: women x 1.6, men x 1.41). Patients with type 2 diabetes who have no evidence of previous coronary heart disease were found to be at the same risk of myocardial infarction and cardiovascular death as non-diabetic patients who had already suffered from a myocardial infarction.

The diabetes subject cohort of the HOPE Study, (Heart Outcomes Prevention Evaluation Study), sought to investigate whether ACE inhibitor treatment with ramipril in high-risk patients with diabetes lowers the risk of cardiovascular events. Within this main study the MICRO-HOPE substudy investigated the effect of ACE inhibitor treatment with ramipril on microalbuminuria and diabetic retinopathy. The aim of this article is to offer a clinical summary of the above studies and suggest recommendations for clinical practice.

Key words: diabetes, cardiovascular disease, microvascular complications, HOPE study, ACE inhibitor.

Methodology
- **Subjects**: People with diabetes age 55 or more with previous history of cardiovascular disease, (coronary artery disease, stroke, peripheral vascular disease) or one cardiovascular risk factor (total cholesterol > 5.2 mmol/L, HDL cholesterol ≤ 0.9 mmol/L, hypertension, known microalbuminuria, current smoking status).
- **Exclusion criteria**: Dipstick positive proteinuria, established diabetic nephropathy, severe renal disease, hyperkalaemia, congestive cardiac failure, low ejection fraction (< 40%), uncontrolled hypertension, recent myocardial infarction or stroke.
- **Sites**: Study conducted in 281 centres in 19 countries in North and South America and Europe, (Argentina, Austria, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Ireland, Italy, Mexico, Netherland, Norway, Spain, Sweden, Switzerland, UK, USA).
- **Ethics**: The HOPE Study protocol was approved locally by Ethics Committees and all subjects provided written informed consent.
- **Study design**: The study was a 2 x 2 design with randomisation of subjects to 10 mg ramipril or placebo taken once-daily in the evening and 400 IU of Vitamin E or placebo daily. Follow-up visits at one month and then every six months. Duration of study was 4.5 years.
- **Treatment**: The initial running period 2.5 mg ramipril for 7–10 days, continued into the study if creatinine concentration 200 µmols or lower and potassium < 5.5 mmol/L or lower.
- **Primary end point**: Development of myocardial infarction, stroke, cardiovascular death.
- **Secondary end point**: Total mortality admission to hospital for congestive cardiac failure, unstable angina, cardiovascular and revascularisation, overt nephropathy, heart failure, worsening angina, development of diabetes in subjects with no history of diabetes.
- **Other points**: Patients were judged to have type 2 diabetes if they developed diabetes at age 30 years or older or were not taking insulin. Hypertension was defined as taking drugs to treat hypertension or blood pressure greater than 160/90 mmHg. MICRO-HOPE Substudy: Urinary albumin excretion measured at baseline one year end of study by the albumin and creatinine ratio in a first morning sample. Microalbuminuria defined as an albumin/creatinine ratio of 2 mg/mmol or higher in men and women. Overt nephropa-
thy defined as 24-hour urine albumin 300 mg or greater or 24-hour urine total protein 500 mg or greater, or albumin/creatinine ratio greater than 36 mg/mmol.

**Statistical analysis**
- This study was adequately powered to detect relative risk reduction in the rate of myocardial infarction, stroke or cardiovascular disease.
- The study was ended six months earlier than the five years planned on the recommendation of the independent data safety and monitoring board.
- Intention to treat analysis.
- Results reported as relative risk reductions, Kaplan-Meier curves to estimate survival. ANOVA analysis adjusted for baseline values. Cox’s regression model for interactions.

**Results**
- There were 9,541 participants in the HOPE Study of which 3,654 had diabetes (39.3%). The results are presented on this group alone. Some patients (n=77) participated in another substudy in which they only received 2.5 mg of ramipril and therefore the main data set is on the 3,577 subjects receiving 10 mg ramipril.
- Mean age 65.4, 37% female, 56% previous history of hypertension. At the end of study 65% in the placebo group and 66% in the ramipril group were still taking the study drugs at the end of the 4.5 years of the study.
- At four years 12% of the ramipril group and 15% of the placebo group were taking open label ACE inhibitors.
- Reasons for stopping ramipril were cough, dizziness, angioedema, hypertension or clinical event.
- The reasons for open label ACE inhibitor use in the placebo group were heart failure, proteinuria or hypertension.

**Primary outcomes**
- Combined primary outcome of myocardial infarction, stroke or cardiovascular death reduced by 25%, (ramipril 15.3% versus 19.8% placebo).
- Myocardial infarction reduced 22%, (ramipril 10.2% versus 12.9% placebo).
- Stroke reduced 33%, (ramipril 4.2% versus 6.1% placebo).
- Cardiovascular death reduced 37%, (ramipril 6.2% versus placebo 9.7%).

**Secondary outcomes**
- Total mortality reduced 24%
- Revascularisation reduced 17%
- Overt nephropathy reduced 24%
- Overt nephropathy, laser, therapy or dialysis reduced 16%.

**Other outcomes**
- Any heart failure reduced 20%. Transient ischaemic attacks reduced 26%. Worsening angina reduced 13%, (p=0.057). The benefit of ramipril was noted irrespective of whether subjects had a history of previous cardiovascular events, hypertension or microalbuminuria, or whether the patients had type 1 or 2 diabetes. At the end of the study there is no significant difference in HbA1c% values.
- Blood pressure difference was 2.47/1.00 in favour of ramipril. After adjustment and changes in blood pressure, ramipril had the same effect on primary outcomes as before adjustment.
- Vitamin E had no significant effect.
- Treatment of 1,000 patients with ramipril for four years will prevent about 150 events in approximately 70 patients.

**Clinical practice comments**
- ACE inhibition significantly reduced the risk of major cardiovascular outcomes by 25–30% in a broad range of patients with diabetes, 55 years of age or greater. These results would apply to the vast majority of our patients with diabetes as 70% have hypertension, another 70% have dyslipidaemia, 20% smoke and 10% have microalbuminuria. The results of the HOPE and MICRO-HOPE study therefore apply to around 85% of patients with diabetes in the study age group.
- Ramipril also reduced the risk of the development of overt nephropathy, renal failure or need for laser treatment. The treatment effect is comparable to other cardiovascular prevention measures such as aspirin prophylaxis, statin treatment for dyslipidaemia and treatment of hypertension.
- The number needed to treat to prevent a major cardiovascular or microvascular event would be 15 high-risk patients with diabetes for 4.5 years to prevent one individual from having a myocardial infarction, stroke, cardiovascular death, admission to hospital for cardiac failure, revascularisation, development of overt nephropathy, laser treatment for sight threatening diabetic retinopathy or renal dialysis. This equates to a drug cost of £11 340 to prevent one of the above events.
- It is probably fair to state that the risk reduction in cardiovascular events is greater than a blood pressure effect alone. However, this requires further close scrutiny as the ramipril group had a distinctly lower blood pressure (by 2.47/1.00 mmHg) with a probable greater effect on the 24-hour ambulatory blood pressure.
- The cardiovascular protective effects of ACE inhibitors may be due to an effect on the endothelium via angiotensin II. The latter is a powerful vasoconstrictor which promotes vascular smooth muscle proliferation by induction of proto-oncogenes and various growth factors. Angiotensin II stimulates the release of endothelin. It also inhibits fibrinolysis and promotes thrombosis. ACE inhibition will therefore reduce plaque rupture and cardiovascular events. Bradykinin which is increased with ACE inhibitor treatment is a vasodilator and would have the opposite effects of angiotensin II.
- The results of this study concord with other studies with ACE inhibitors. For example the Captopril Prevention Project which found 14% reduction in rate of myocardial infarction, stroke or cardiovascular death in patients taking
captopril. However other studies have shown no distinct benefit of ACE inhibitors over beta blockers.

- The beneficial effect of ramipril was independent of whether the subject was already taking cardiovascular disease prevention agents such as aspirin, beta blockers or lipid-lowering agents.
- With respect to microvascular outcomes, these results concord with the results of the Eurodiab Controlled trial of Lisinopril in insulin-dependent diabetes (EUCLID) nephropathy and the EUCLID retinopathy studies (using lisinopril 20 mg od), although these were type 1 diabetes mellitus patients only. Microvascular complications may have improved due to a beneficial effect on microvascular autoregulation.
- The HOPE Study contained a comparable number of patients as the UKPDS in an equally well designed study. The results should therefore be taken seriously with the findings implemented in clinical practice. Ramipril now has a license for reducing the risk of myocardial infarction/cardiovascular disease or need for revascularisation procedures in diabetic patients of 55 years or more who have one or more of the following clinical findings: Hypertension (greater than 160/90 mmHg), dyslipidaemia, cholesterol (greater than 5.2, HDL < 0.9), current smoker, known microalbuminuria, clinical evidence of previous vascular disease. Other indications for ACE inhibitors including mild to moderate hypertension, congestive cardiac failure as adjunct to diuretic therapy and reduction in mortality in patients surviving acute myocardial infarction with clinical evidence of heart failure. Lisinopril

**Table 1.** A strategy to reduce cardiovascular mortality in diabetes care

<table>
<thead>
<tr>
<th>Primary prevention by treatment of cardiovascular risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Exercise, healthy diet, obesity management, smoking cessation</td>
</tr>
<tr>
<td>- Control of hypertension (BP ≤ 140/80)</td>
</tr>
<tr>
<td>- Glycaemic control (HbA1C ≤ 7%)</td>
</tr>
<tr>
<td>- Cholesterol reduction with statins (T. chol ≤ 5.0, LDL ≤ 3.0, HDL ≥ 0.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary prevention of cardiovascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Aspirin 75 mg od</td>
</tr>
<tr>
<td>- Beta blockers</td>
</tr>
<tr>
<td>- ACE inhibitors</td>
</tr>
<tr>
<td>- Intensive insulin therapy (Digami protocol)</td>
</tr>
<tr>
<td>- Cholesterol reduction with statins</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Other preventive measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Ramipril 10 od (HOPE study)</td>
</tr>
<tr>
<td>- Aspirin 75 mg od</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical treatment of coronary heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Intervventional cardiology</td>
</tr>
<tr>
<td>- Surgical</td>
</tr>
</tbody>
</table>

**Figure 1.** HOPE - Primary outcomes

![Graph showing primary outcomes](image)

**Figure 2.** HOPE - Secondary outcomes

![Graph showing secondary outcomes](image)

**Figure 3.** HOPE - Other outcomes

![Graph showing other outcomes](image)
also has a licence for prevention of nephropathy in albuminuric patients with normotensive type 1 diabetes and hypertensive type 2 diabetes.

- Rather than risk reductions from a health planning point of view, it is probably better to look at number needed to treat (NNT) to prevent an event. NNT is calculated as 100%/absolute % reduction in risk and denotes the number of subjects who must receive the study treatment to prevent one event. To illustrate its use, consider treatment A which reduces risk of Event X from 10% per year to 5% (also a risk reduction of 50%). The NNT is 100%/10–5 = 20 per year. Now consider treatment B which reduces risk of Event Y from 1% per year to 0.5% (also a risk reduction of 50%). The NNT is 100%/1.0–0.5 = 200 per year. Clearly the NNT is a valuable concept in considering treatment effects and calculating costs of healthcare. The risk reduction and NNTs for the main outcomes are shown in figures 1–3.

- NNTs are shown in graphs 1, 2 and 3 with comparisons to the main United Kingdom Prospective Diabetes Study (UKPDS) studies shown in table 1.

### How to use ramipril

2.5 mg once a day for one week, 5 mg for three weeks and then 10 mg daily. In clinical practice ramipril is frequently given 5 mg od for one week followed by 10 mg od. Urea, potassium and creatinine levels should be checked after 2–4 weeks on ACE inhibition with the ACE inhibitor discontinued if the urea rises by 50% or more or if the creatinine rises by more than 20%. Attention to other drugs which worsen renal parameters (diuretics and other vasodilators) may allow continued use of ACE inhibitors.

### Conclusion

At the average age of diagnosis of diabetes (55 years), the estimated life expectancy is reduced by seven years in women and five years in men, 80% of these premature deaths are due to cardiovascular disease. All diabetes care programmes should aim to reduce cardiovascular disease by an aggressive strategy to decrease blood pressure to the target of 140/80 mmHg or lower, improve glycaemic control to a target HbA1C of 7% or lower, lipid lowering (total cholesterol < 5 mmol/L, LDL < 3 mmol/L, HDL > 0.9 mmol/L), smoking cessation, aspirin treatment, together with due attention to healthy eating, exercise and weight reduction. The HOPE and MICRO-HOPE Study clearly shows the beneficial effect of adding an ACE inhibitor into this strategy (table 2).

### Tables

#### Table 2. Risk reductions and NNT values for recent large trials in diabetes care

<table>
<thead>
<tr>
<th>End point</th>
<th>UKPDS-glycaemic control trial</th>
<th>UKPDS-metformin subtrial</th>
<th>UKPDS-Hypertension trial</th>
<th>HOPE MICRO-HOPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>any Diabetes end point</td>
<td>RR</td>
<td>nnt/yr</td>
<td>RR</td>
<td>nnt/yr</td>
</tr>
<tr>
<td>Death from diabetes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Death from all causes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.7%</td>
<td>370</td>
<td>7%</td>
<td>143</td>
</tr>
<tr>
<td>Stroke</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Microvascular complications</td>
<td>2.8%</td>
<td>357</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* overt nephropathy, laser therapy, or dialysis; RR = risk reduction; nnt = number needed to treat


