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Department of Cardiovascular Medicine,
John Radcliffe Hospital,
Headley Way,
Oxford, OX3 9DU,
UK

Correspondence to:
Professor Peter Sleight
Tel: +44 1865 760564
Fax: +44 1865 768844

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The HOPE Study (Heart Outcomes Prevention Evaluation)

Peter Sleight

Introduction

The rationale for using ACE inhibitors in high risk subjects with preserved left ventricular (LV) function was based on the large body of experimental evidence which supported the concept that angiotensin II had deleterious effects on proliferation of vascular smooth muscle, on LV mass, and on endothelial function, in addition to effects on blood pressure (BP). This experimental promise was first supported in man by the unexpected reduction in myocardial infarction (MI) which was seen in a meta analysis[1] of the SOLVD[2,3] and SAVE[4] studies using enalapril and captopril respectively, in subjects with heart failure and with LV dysfunction following MI.The HOPE (Heart Outcome Prevention Evaluation) study was designed to test the hypotheses that two preventative intervention strategies, namely ACE inhibition or vitamin E would improve morbidity and mortality in high risk patients compared with placebo.The initial three papers from the HOPE investigators were published recently in the New England Journal of Medicine[5,6] and the Lancet.[7] The NEJM articles describe the main results of the Vitamin E and ACE inhibitor (ramipril) arms of the study, while the Lancet article (MicroHOPE) describes the results of these interventions in the large diabetic sub-population in HOPE.
This review addresses the results of the ACE inhibitor arm of the study, both on the trial population as a whole and on the large diabetic subgroup.

Trial design

HOPE was a large simple factorial-design, placebo-controlled trial which tested these two plausible strategies for the prevention of cardiovascular events in over 9,500 patients, who were considered at high risk of future vascular death or morbidity by reason of age, (>55 years), evidence of prior vascular events or existing vascular disease, or diabetes. Diabetics were required to have either known vascular disease or one other risk factor for cardiovascular disease, e.g. cigarette smoking, BP greater than 140/90, or elevated cholesterol (>5.2 mmol/L).
Patients already on treatment with Vitamin E or an ACE inhibitor, or for whom an ACE inhibitor was indicated (e.g. heart failure or LV dysfunction) were excluded.
It is important (especially in the context of wider use of ACE inhibitors in high risk subjects in general practice) to note that the protocol of HOPE included a run-in period during which all 10,576 initially eligible subjects took a small dose of 2.5 mgs of active ramipril for 7-10 days, followed by matching placebo for 10-14 days. This was in order to exclude side effects, non-compliant patients (or withdrawal of consent) and to check for abnormal serum electrolytes or creatinine. 1035 patients were excluded for these reasons.
The remaining 9541 subjects were then allocated to ramipril or placebo, beginning with a titration phase of 2.5 mg/day for 1-week, 5 mg/day for 3-weeks, and thereafter 10 mg/day.
Follow-up was at 1-month and thereafter 6-monthly.
This editorial will focus on the striking results of the ACE inhibitor arm of the study.

A high risk, but well treated population

The study was unusual in that the trial interventions were added, in the majority of subjects, to other proven medication, which would be expected to reduce the impact of the trial regimens.At baseline, 76% of the subjects were on an anti-platelet agent (mostly aspirin), 40% on a beta-blocker, 45% on a calcium channel blocker, 15% on a diuretic and 30% on a lipid lowering agent. During the 4.5 years of the trial, the use of lipid lowering drugs, beta-blockers and diuretics increased, whilst that of calcium channel blockers decreased by 5%.
Perhaps as a result of background medication, the baseline BP was normal at 139/79 mmHg, despite a history of hypertension in almost half the trial population.The reduction in BP caused by ramipril (titrated from 2.5 -> 10 mg, with 82% at 1-year and 65% at the final visit taking the full dose), was modest: a difference of about 3-4 mmHg systolic and 1-2 mmHg diastolic BP between ramipril and placebo allocated subjects over the study period.
Thus the rampiril arm of the HOPE trial differs from many trials in hypertension in that (a) the baseline BP was normal or near-normal, (b) the treatment-induced reduction in BP was modest and (c) there was extensive use of concomitant anti-hypertensive, anti-platelet and lipid lowering drugs at baseline, although these were evenly distributed between the ramipril and placebo groups.

Results

The HOPE Study showed that ramipril was well tolerated, with the large majority of patients continuing on the full 10 mg dose. There was only a 5% excess drop out (because of cough) in the ramipril group.
The primary end point was defined as a combination of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.
The trial was stopped early (after 4.5 years) on the advice of the Data Monitoring Committee because of the consistent and overwhelming evidence of benefit in the ramipril allocated group.
During the study period, 17.8% of subjects in the placebo group reached the primary combined endpoint, compared with 14% in the ramipril-treated group. This represents a reduction in relative risk of 22% with unusually tight confidence intervals (RR 0.70-0.86, p=<0.001) The individual components of the composite end point were also reduced highly significantly by 32% for stroke, 20% for MI and 26% for cardiovascular death. Ramipril also significantly reduced the relative risk of experiencing several other clinical endpoints including heart failure (by 23%) and revascularisation procedures

(by 15%). All cause mortality was reduced by 16% (p = 0.005). The Kaplan-Meier event curves diverged by one year and continued diverging until the trial end.
Non-cardiovascular mortality was reassuringly equal in the ramipril and placebo groups.A remarkable feature of the results was their consistency over a wide range of pre-specified sub-group analyses e.g. those with or without: diabetes, history of hypertension, prior overt vascular disease, those above or below 65 years, male or female.
The results were similar irrespective of concomitant baseline hypotensive agents, and whether or not they were taking either beta-blockers, calcium channel blockers or diuretics, or lipid lowering agents.
An unexpected finding in HOPE was that ramipril-allocated patients experienced a 33% reduction in the onset of new diabetes during the 4.5 years of the trial, supporting the similar, though less pronounced, reduction in new diabetes reported in the Captopril Prevention Project (CAPP) study.[8] Since this was not a pre-specified end point this finding should therefore be regarded as a pointer for further research, and requires confirmation in other studies.

Evidence for a non-blood pressure mechanism of benefit

The reduction in event rates, particularly for MI, was much greater than would have been expected from such a modest fall in BP caused by ramipril. The much-quoted meta analysis of blood pressure lowering trials using older agents would suggest a reduction in stroke of approximately 38% and in MI of only 16% when diastolic blood pressure is reduced by 4-5 mmHg over a period of 4-5 years.HOPE achieved this with a much more modest diastolic BP reduction of 1-2 mmHg. It has been argued that the high risk population enrolled in the HOPE study might, by reason of additional risk factors, have a steeper BP/risk gradient, that is a higher event rate for a given level of blood pressure, than the lower risk subjects generally recruited in the earlier hypertension trials. However the risk reduction in the ramipril group was much greater than would have been inferred from the BP/risk gradient seen in the placebo arm of HOPE. Further evidence to support a major non-blood pressure effect of ramipril is provided by a multiple regression analysis of the diabetics in the HOPE Study,[7] which showed similar relative risk reductions even after allowing for the effect of the reduction in blood pressure.
When the benefits from ramipril were related to quartiles of baseline BP, greater risk reduction was shown in patients with higher baseline systolic BP (unpublished data). However it is important to realise that increasing BP levels tend to co-exist with increases in other risk factors such as age, body mass index, incidence of diabetes and prior cardiovascular events including stroke.

The Micro-HOPE Study

The results on the 3577 diabetic subjects enrolled in the HOPE Study[7] were even more striking than those of the main study, with highly significant relative risk reductions of 25% for the combined primary outcome, 22% for MI, 33% for stroke and 37% for cardiovascular death. Importantly overt nephropathy was reduced by 24%. Laser therapy for retinopathy was non-significantly reduced by 22%.
As in the main study, there was again consistency of benefit in many sub-groups. For example those with or without microalbumenuria at baseline, those with or without a history of hypertension at baseline, those with type I or type II diabetes, or those on different modes of hypoglycaemic therapy (insulin or oral hypoglycaemic agents).

Mechanisms of benefit from ramipril

These results argue for a vasculo-protective effect of ramipril on top of the benefit to be expected from the modest reduction in BP. Possible mechanisms may include reduction in the angiotensin II-induced intimal and vascular smooth muscle proliferation. The relatively rapid benefit might also support a putative role in plaque stabilisation, perhaps by reduction of cytokines and macrophage activity by lowered levels of angiotensin II.

A Class effect?

The rationale of the HOPE Study was based on the known actions of angiotensin II and also on the meta analysis of the SOLVD and SAVE trials. It is therefore likely that the benefits of ramipril in the HOPE study are due to a class effect on ACE inhibition. However, as previously noted by Francis,[9] these results with a long-acting ACE inhibitor with good tissue penetration, given at high doses, may not be applicable across the range of available ACE inhibitors,with varying physico-chemical properties, given at different doses, or indeed to angiotensin receptor antagonists. On-going trials will answer this question definitively.

Implications for treatment of hypertension

Recent trials such as the Hypertension Optimal Treatment (HOT) Study[10] and the UK Prospective Diabetes Study (UKPDS)[11] have emphasised that, in order to reduce BP to below 140/90, it is necessary, in the majority of cases, to use combination therapy with two or more agents and so arguments about the merits of one class of drug versus another are somewhat dated. The HOPE results certainly show that it is both safe and beneficial to lower BP in the normal range, especially in populations with known coronary disease, supporting the advice in recent guidelines. The HOPE results also support the use of ACE inhibitors for the treatment of hypertension, which previously had lacked large mortality data in hypertensive subjects.
It might be argued that the recent comparisons in the STOP-2 Study[12] suggest no superiority of ACE inhibitors over other agents. Very similar reductions in events were seen in elderly patients with isolated systolic hypertension receiving a dihydropyridine calcium channel blocker compared with placebo in the SYST-EUR trial.[13] However the subjects in both these studies had very much higher entry BP (of the order of 200 mmHg systolic) and the treatment-induced reduction in BP was much larger than in the HOPE Study (e.g. 35/17 mmHg in STOP-2). The HOPE Study adds the information that, in well-controlled hypertensive subjects with known vascular disease or diabetes, the addition of ramipril confers substantial additional benefits, in addition to those of beta-blockers or calcium channel blockers. The authors of the STOP-2 report comment that patients in the ACE inhibitor arm of STOP-2 experienced significantly less heart failure or myocardial infarctions than in the calcium channel or beta-blocker/diuretic arms.[12]

Clinical implications of the HOPE Study

These results show substantial benefits in mortality and morbidity from the use of ramipril in a large group of subjects at high risk of future cardiovascular events; the results are also unusually clear and consistent and were achieved on top of current conventional treatment.
Although many of the subjects had experienced a previous myocardial infarction, this was more than one year

before enrolment in 80%, and furthermore these subjects had good ventricular function. Such patients are common in both general and hospital practice. The implications for diabetic patients are particularly striking.

These results should greatly extend the use of ACE inhibition to a wider group of patients i.e. not only those with LV dysfunction, hypertension or diabetes with albuminuria - for which ACE inhibition is already proven - but to those patients who are currently given prophylaxis with aspirin (as were most of the HOPE population). Preliminary analyses of the HOPE data suggest this will be highly cost effective.

It is clear that current recommendations for the use of ACE inhibitors, which focus mainly on vasodilatation and/or ventricular remodelling should be broadened.

Organisation and support

The study was organised, coordinated and independently analysed by the Canadian Cardiovascular Collaboration Project Office in McMaster University, Hamilton, Ontario. The chair of the Steering Committee was S. Yusuf, co-chairs G. Dagenais and P. Sleight. Recruitment was from North and South American and European in 19 European countries. It was funded by the Medical Research Council of Canada, Hoechst-Marion-Roussel, AstraZeneca, King Pharmaceuticals, Natural Source Vitamin E Association and Negma, and the Heart and Stroke Foundation of Ontario.

The clear results are in no small part due to the judgement of the independent Data Safety and Monitoring Board: D. Sackett (chair), R. Collins, E. Davis, C. Furberg, C. Hennekens, B. Pitt,and the late R. Turner.

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