Use of ramipril in preventing stroke: double blind randomised trial

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Abstract

Objective To determine the effect of the angiotensin converting enzyme inhibitor ramipril on the secondary prevention of stroke.
Design Randomised controlled trial with 2 × 2 factorial design.
Setting 267 hospitals in 19 countries.
Participants 9297 patients with vascular disease or diabetes plus an additional risk factor, followed for 4.5 years as part of the HOPE study.
Outcome measures Stroke (confirmed by computed tomography or magnetic resonance imaging when available), transient ischaemic attack, and cognitive function. Blood pressure was recorded at entry to the study, after 2 years, and at the end of the study.
Results Reduction in blood pressure was modest (3.8 mm Hg systolic and 2.8 mm Hg diastolic). The relative risk of any stroke was reduced by 32% (156 *v* 226) in the ramipril group compared with the placebo group, and the relative risk of fatal stroke was reduced by 61% (17 *v* 44). Benefits were consistent across baseline blood pressures, drugs used, and subgroups defined by the presence or absence of previous stroke, coronary artery disease, peripheral arterial disease, diabetes, or hypertension. Significantly fewer patients on ramipril had cognitive or functional impairment.
Conclusion Ramipril reduces the incidence of stroke in patients at high risk, despite a modest reduction in blood pressure.

Introduction

Stroke is the second leading cause of death in the world and of disability in developed countries.[1–4] In North America, 550 000 new strokes occur each year and there are approximately five million people who have had a stroke, 60% of whom have some residual disability.[4 5] Stroke is also responsible for a substantial proportion of deaths and disability in developing countries.[6] Strokes can be prevented by lowering blood pressure in people with hypertension and by the use of antiplatelet agents in people with vascular disease.[7 8] Although a person's risk of stroke increases with blood pressure, the population attributable risk of stroke is greatest at pressures that would not currently be treated with drugs.[9] We therefore need additional strategies that lower the risk of stroke across a broad range of patients at high risk.

Angiotensin converting enzyme inhibitors have been shown to block the activation of the renin-angiotensin system in the plasma as well as in the vascular wall. Recent experimental and human data suggest that angiotensin converting enzyme inhibitors reduce proliferation of vascular smooth muscle; enhance endogenous fibrinolysis; have the potential to stabilise plaques; and decrease angiotensin II mediated atherosclerosis, plaque rupture, and vascular occlusion.[10] Angiotensin converting enzyme inhibitors therefore have the potential to lower the risk of ischaemic vascular events, including strokes, through mechanisms that are independent of lowering blood pressure.

We provide a detailed analysis of the impact of ramipril, an angiotensin converting enzyme inhibitor, on stroke, its subtypes, and the related disability and report the effects in various subgroups of patients in the heart outcomes prevention evaluation (HOPE) study.

Design and methods

The HOPE study was a double blind randomised trial with a two by two factorial design, in which participants were randomised to receive up to 10 mg of ramipril, 400 IU of vitamin E, both, or matching placebos.[11] We provide a brief outline here.

Participants

Participants were aged 55 or over and were at high risk of cardiovascular events because of previous coronary artery disease, cerebrovascular disease, or peripheral arterial disease or diabetes plus one additional risk factor. Patients were excluded if they were taking either an angiotensin converting enzyme inhibitor or vitamin E; had heart failure or a known left ventricular ejection fraction of less than 0.40, known proteinuria, or uncontrolled hypertension; or had had a previous stroke or a myocardial infarction less than one month before enrolment in the study. Informed consent was obtained from all participants before enrolment in the study, and the study was approved by the ethics committee at each centre.

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Intervention

Eligible patients entered a run-in phase in which they received 2.5 mg ramipril daily for 7-10 days, after which serum creatinine and potassium levels were measured. Participants then started a 10-14 day course of placebo. Those who tolerated and adhered to this regimen were then randomised to receive either placebo or 2.5 mg ramipril daily for one week, followed by placebo or 5.0 mg ramipril for a further three weeks. One month after randomisation the patient's serum creatinine and potassium were measured; if these were satisfactory the patient continued on either placebo or 10 mg ramipril for the remainder of the study. Participants were seen after six months and then every six months until the end of the study, with an average follow up of 4.5 years.

Of the 10 576 patients who entered the run-in phase, 1035 were not randomised because of non-adherence, side effects, or withdrawal of consent; 244 patients were entered into a substudy of 2.5 mg ramipril and are not included in this paper. Outcome results were available on 9539 (99.9%) of the 9541 patients randomised. The first participant was recruited in December 1993. The originally scheduled completion date was November 1999, but the ramipril arm of the study was terminated early (April 1999) because of clear benefit.

Outcome measures

The primary outcome was the composite end point of myocardial infarction, stroke, or cardiovascular death.[12] The individual components of this composite end point were analysed separately. All outcomes were adjudicated by a central committee. This analysis focuses on stroke.

Investigators reported the occurrences of stroke or transient ischaemic attack at follow up visits. For every stroke reported, information on the stroke, including symptoms and functional impairment, was documented. The investigators used a simple six point scale to record if there was full recovery, persistent symptoms, some functional impairment, functional impairment necessitating the assistance of others to perform activities of daily living, or inability to perform activities of daily living even with help at seven days or at discharge if earlier. Discharge summaries, consultation notes, and results of computed tomography or magnetic resonance imaging were documented. A central committee adjudicated all strokes on the basis of predetermined definitions. Classification of a stroke as either ischaemic or haemorrhagic was confirmed by computed tomography or magnetic resonance imaging within 14 days of onset or by autopsy. All other strokes were classified as being of uncertain aetiology. Computed tomography, magnetic resonance imaging, or autopsy results were obtained for 84% of strokes.

Blood pressure was measured at entry to the study, after two years, and at the end of the study. Two measurements were taken on each arm after the patient had been supine for five minutes. The lowest measurements on each arm were averaged to obtain the systolic and diastolic values that were recorded.

Statistical analysis

The study had 90% power to detect a 13.5% reduction in relative risk for the primary outcome, with an annual event rate of 4% in 9000 patients studied for five years. Assuming a stroke rate of 1.2% per year in the control group for five years, the study had 80% power to detect a 22.0% reduction in the relative risk of stroke with a two sided α level of 0.05 in an intention to treat analysis. We estimated survival curves according to the Kaplan-Meier procedure and compared treatments by using the log rank test.[13] Because of the factorial design, we stratified all analyses for the randomisation to vitamin E or placebo. We conducted subgroup analyses by using tests for interactions in the Cox regression model. We used this model to estimate the reduction in relative risk and the 95% confidence intervals associated with ramipril treatment in unadjusted analyses and after controlling for changes in blood pressure.

The data and safety monitoring board monitored the study. Monitoring boundaries for the study were four standard deviations between the two groups in terms of benefit of ramipril in the first half of the study and three standard deviations in the second half. For harm, the boundaries were three standard deviations in the first half of the study and two standard deviations in the second half. Because of clear benefit, the study was terminated on 22 March 1999.

Study organisation

The study was conducted in 267 hospital clinics in 19 countries. It was coordinated by the Canadian Cardiovascular Collaboration in Hamilton, Canada.

Results

Baseline characteristics

The baseline characteristics of the HOPE population have been described elsewhere.[14] Patients were on average 66 (SD 7) years old and had a mean systolic blood pressure of 139 (20) mm Hg and a mean diastolic blood pressure of 79 (11) mm Hg. Seven thousand four hundred and seventy seven (80%) patients had a history of coronary artery disease, 1013 (11%) had previous stroke or transient ischaemic attack, 4051 (43%) had peripheral arterial disease, 3577 (38%) had diabetes, and 4355 (46%) had hypertension; 7074 (76%) patients were taking aspirin or other antiplatelet agents, and 2658 (28%) were taking lipid lowering agents.

Changes in blood pressure

Blood pressure decreased on average by 3.8 mm Hg systolic and 2.8 mm Hg diastolic in the ramipril group and by 0.66 mm Hg systolic and 1.1 mm Hg diastolic in the placebo group. The mean baseline blood pressure of participants who developed a stroke was 143/79 mm Hg compared with 139/79 mm Hg in patients who did not have a stroke.

Incidence of stroke and transient ischaemic attacks

A total of 156 (3.4%) patients in the ramipril group had a stroke compared with 226 (4.9%) in the placebo group (relative risk 0.68, 95% confidence interval 0.56 to 0.84; $P = 0.0002$). Seventeen (0.4%) patients in the ramipril group had a fatal stroke compared with 44 (1.0%) in the placebo group (0.39, 0.22 to 0.67). Non-fatal stroke occurred in 139 (3.0%) patients in the ramipril group and 182 (3.9%) in the placebo group (0.76, 0.61 to 0.94).

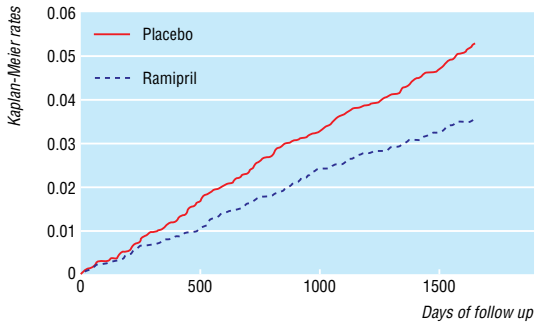

Fig 1 Kaplan-Meier estimates of the development of stroke by treatment group. The relative risk of developing stroke in the ramipril group compared with the placebo group was 0.68 (95% confidence interval 0.56 to 0.84; P=0.0002).

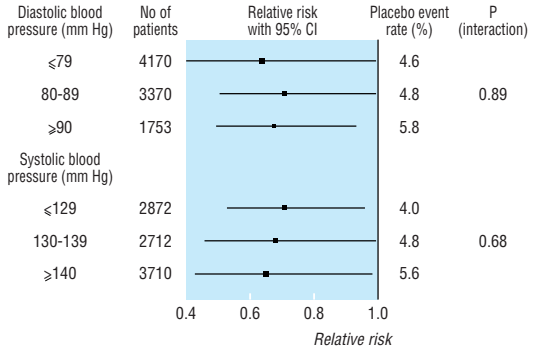

Fig 2 Impact of ramipril on stroke based on baseline blood pressure

In the first year 36 (0.8%) stroke events occurred in the ramipril group and 53 (1.1%) in the placebo group (0.68, 0.45 to 1.04). By year two 77 (1.7%) stroke events had occurred in the ramipril group and 112 (2.4%) in the placebo group (0.69, 0.51 to 0.92). At year three 113 (2.4%) patients taking ramipril had had a stroke compared with 163 (3.5%) taking placebo (0.69, 0.54 to 0.88), and by the fourth year 142 (3.1%) patients in the ramipril group and 207 (4.5%) in the placebo group had had a stroke (0.68, 0.55 to 0.84) (fig 1). In addition, fewer patients had multiple strokes in the ramipril group than in the placebo group (24 *v* 34).

A total of 190 (4.1%) patients in the ramipril group had a transient ischaemic attack compared with 227 (4.9%) in the placebo group (0.83, 0.68 to 1.00; P = 0.052). Patients taking ramipril had a significantly reduced combined risk of stroke and transient ischaemic attack (n = 315, 6.8%) compared with those on placebo (405, 8.7%) The relative risk was 0.77 (0.66 to 0.89; P = 0.0004).

Outcome by type of stroke

Table 1 shows the results subdivided by type of stroke. Fewer patients (101, 2.2%) in the ramipril group than in the placebo group (157, 3.4%) had an ischaemic stroke (relative risk 0.64, 0.50 to 0.82), a haemorrhagic stroke (12 (0.26%) *v* 16 (0.34%); 0.74, 0.35 to 1.57), or a stroke of uncertain origin (52 (1.1%) *v* 65 (1.4%); 0.79, 0.55 to 1.14).

Functional and cognitive outcomes

Tables 1 and 2 show the effect of ramipril on functional and cognitive outcomes. Significantly fewer patients on ramipril than on placebo had functional impairment, particularly in terms of cognition, motor weakness, speech, and swallowing.

Results by baseline blood pressure and in other subgroups

The beneficial treatment effects were consistently seen regardless of baseline blood pressure (fig 2). Furthermore, a 28% reduction in relative risk was seen after both baseline blood pressure and change in blood pressure had been controlled for. The benefits of ramipril were evident in all the subgroups examined (figs 3 and 4).

Discussion

Our results show that prolonged treatment with ramipril is effective in reducing fatal and non-fatal stroke and transient ischaemic attack in a broad group of patients at high risk of stroke but with relatively normal blood pressure. The impact is seen early, and the benefit continues to increase throughout the study period. The reduction is consistent across different subtypes of stroke and in various subgroups examined and is independent of the modest reduction in blood pressure seen with ramipril.

Benefit was seen at all values of diastolic and systolic blood pressure, including in patients with an initial blood pressure of less than 120 mm Hg systolic or less than 70 mm Hg diastolic, confirming that the beneficial effect of ramipril is not confined to those with "high" blood pressure. Angiotensin converting enzyme inhibitors have multiple mechanisms, in addi-

Table 1 Impact of ramipril on stroke subdivided by non-fatal and fatal stroke, subtype of stroke, and presence or absence of functional impairment. Values are numbers (percentages) unless stated otherwise

Outcome	Ramipril (n=4645)	Placebo (n=4652)	Relative risk (95% CI)
Total strokes	156 (3.4)	226 (4.9)	0.68 (0.56 to 0.84)
Non-fatal:	139 (3.0)	182 (3.9)	0.76 (0.61 to 0.94)
No functional impairment	49 (1.1)	80 (1.7)	0.61 (0.43 to 0.87)
Some functional impairment*	85 (1.8)	108 (2.3)	0.78 (0.59 to 1.04)
Fatal	17 (0.4)	44 (1.0)	0.39 (0.22 to 0.67)
Subtype of stroke			
Ischaemic	101 (2.2)	157 (3.4)	0.64 (0.50 to 0.82)
Non-ischaemic†:	63 (1.4)	78 (1.7)	0.80 (0.57 to 1.12)
Haemorrhagic	12 (0.26)	16 (0.34)	0.74 (0.35 to 1.57)
Uncertain aetiology	52 (1.1)	65 (1.4)	0.79 (0.55 to 1.14)

*Any impairment from functional impairment that does not limit daily activities to assistance needed for all activities of daily living.
†Stroke of haemorrhagic or uncertain aetiology.

Table 2 Details of cognitive and motor changes (24 hours after stroke) associated with stroke in patients with an event.* Values are numbers (percentages) unless stated otherwise

Outcome	Ramipril (n=4645)	Placebo (n=4652)	Relative risk (95% CI)
Change in cognition	28 (0.6)	47 (1.1)	0.59 (0.37 to 0.94)
Change in consciousness	19 (0.4)	28 (0.6)	0.67 (0.38 to 1.20)
Ocular or visual symptoms	30 (0.7)	33 (0.7)	0.90 (0.55 to 1.47)
Weakness in face or limb	92 (2.0)	127 (2.7)	0.72 (0.55 to 0.94)
Sensory symptoms	51 (1.1)	45 (1.0)	1.12 (0.75 to 1.67)
Dysarthria/dysphasia	49 (1.1)	71 (1.5)	0.68 (0.48 to 0.98)
Dysphagia	19 (0.4)	33 (0.7)	0.57 (0.32 to 1.0)

*Data were collected for all but 11 patients who had a stroke; five of the 11 died.

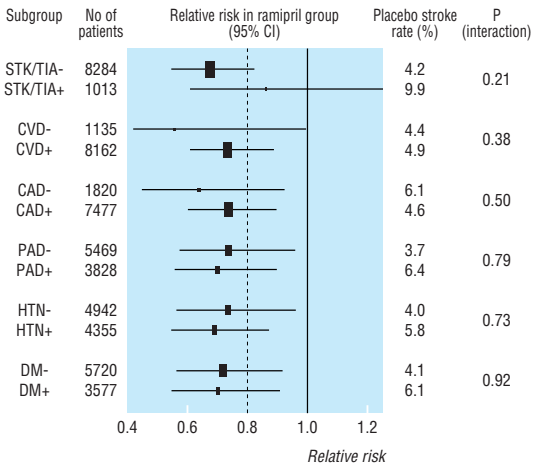

Fig 3 Impact of ramipril on stroke rates among subgroups of patients with different baseline conditions. ('–' indicates absence of condition; '+' indicates presence of condition; STK/TIA=stroke or transient ischaemic attack; CVD=cardiovascular disease; CAD=coronary artery disease; PAD=peripheral arterial disease; HTN=hypertension; DM=diabetes mellitus)

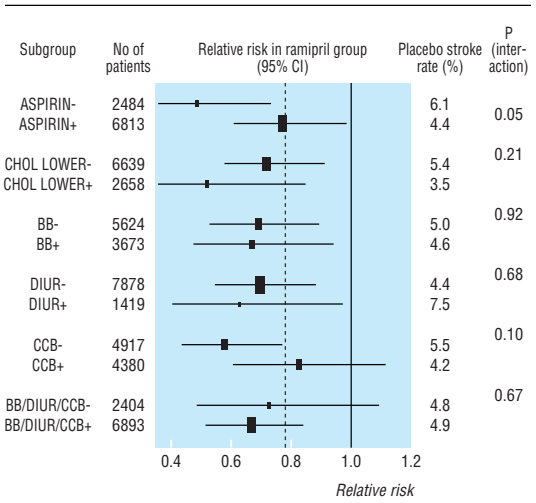

Fig 4 Impact of ramipril on stroke in subgroups of patients based on baseline drug use. *Interaction statistic derived from χ^2 test. ('–' indicates absence of condition; '+' indicates presence of condition; CHOL LOWER=cholesterol lowering agent; BB=β blocker; DIUR=diuretic; CCB=calcium channel blocker)

tion to blood pressure lowering, by which they could prevent atherosclerotic events.[10] The study to evaluate carotid ultrasound with ramipril and vitamin E (SECURE) showed a dose dependent (but blood pressure independent) reduction in carotid artery intimal medial thickness.[15] Furthermore, a recent analysis of the United Kingdom prospective diabetes study (UKPDS) showed that the benefits seen with an angiotensin converting enzyme inhibitor (and β blocker) were substantially larger than predicted from differences in blood pressure alone.[16]

Ramipril reduced not only the number of patients who had a stroke but also the fatality associated with stroke as well as functional impairment in non-fatal stroke. As stroke is the leading cause of disability in developed countries, even moderate decreases in disability would be of global importance.

What is already known on this topic

Treatment with aspirin and lowering blood pressure reduce the incidence of stroke

What this study adds

Ramipril, an angiotensin converting enzyme inhibitor, reduces strokes in patients at high risk whose blood pressure is not elevated, despite only a modest lowering of blood pressure

The benefits are observed even when patients receive aspirin and other blood pressure lowering treatments

The reduction in strokes was consistent across the various subgroups examined, including patients receiving antiplatelet treatment and lipid lowering drugs. The benefits of ramipril are consistent in patients with and without previous stroke, previous manifestation of any cerebrovascular disease, coronary artery disease, peripheral arterial disease, or diabetes. This suggests that our results are broadly applicable to patients at high risk of stroke with diverse presentations and a range of background treatments.

The perindopril protection against recurrent stroke study (PROGRESS) recently reported that perindopril in combination with indapamide reduced the risk of recurrent strokes by 28% in patients with previous cerebrovascular disease.[17 18] The initial blood pressure in this study was higher than in HOPE, and by design the blood pressure was lowered more substantially (−9 mm Hg systolic *v* −3 mm Hg in HOPE). Taken together, these studies clearly document the benefits of an angiotensin converting enzyme inhibitor in both primary and secondary prevention, even in patients without hypertension.

Conclusions

Our results indicate that patients who are at high risk of stroke should be treated with ramipril, irrespective of their initial blood pressure levels and in addition to other preventive treatments such as blood pressure lowering agents or aspirin. Widespread use of an angiotensin converting enzyme inhibitor such as ramipril in patients at high risk of stroke is likely to have a major impact on public health.

Contributors: JB assisted in protocol design, coordinated all aspects of study conduct, assisted with analyses, participated in writing the paper, and is the guarantor. SY formulated the study question, developed the study protocol, was the principal investigator of the HOPE study (responsible for all study related activities), and participated in analysis and writing the paper. JP was the senior statistician responsible for all analyses during the study and contributed to writing the paper. EL participated in the design and execution of the study, provided background rationale for this paper, and contributed to all other aspects of the paper. PS was the European co-chair of the study and was responsible for all aspects of study conduct within Europe, as well as leading the blood pressure reduction analyses and contributing to the paper. BR was involved in protocol design and contributed to the paper. RD was co-chair of the publications committee for the study and participated in the writing of the paper. JO provided input into core ideas and interpretation of findings and edited the paper. JP was the US co-chair of the study, assisted in protocol development, provided

guidance on the current state of the literature, and participated in the writing of the paper.

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