

## 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.<sup>1-4</sup> 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.<sup>4,5</sup> Stroke is also responsible for a substantial proportion of deaths and disability in developing countries.<sup>6</sup> Strokes can be prevented by lowering blood pressure in people with hypertension and by the use of antiplatelet agents in people with vascular disease.<sup>7,8</sup> 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.<sup>9</sup> 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.<sup>10</sup> 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.<sup>11</sup>

### 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.

### Intervention

After a run-in phase in which patients received 2.5 mg ramipril daily for 7-10 days, serum creatinine and potassium levels were measured. Participants then started a 10-14 day course of placebo. Those who

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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, 9541 were randomised and outcome results were available on 9539 (99.9%).

### Outcome measures

The primary outcome was the composite end point of myocardial infarction, stroke, or cardiovascular death.<sup>12</sup> This analysis focuses on stroke.

Investigators reported the occurrences of stroke or transient ischaemic attack at follow up visits. 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. Classification of a stroke as either ischaemic or haemorrhagic was confirmed for 84% of strokes 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.

### Statistical analysis

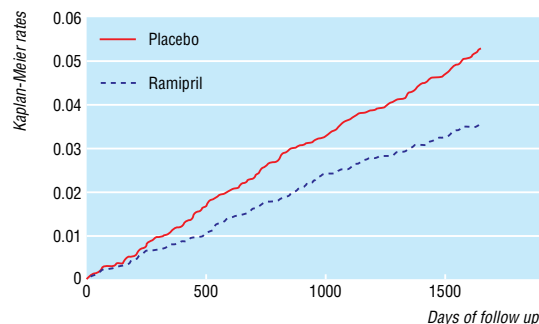
We estimated survival curves according to the Kaplan-Meier procedure and compared treatments by using the log rank test.<sup>13</sup> Because of the factorial design, we stratified all analyses for the randomisation to vitamin E or placebo. We conducted subgroup analyses by using tests for interactions in the Cox regression model.

### 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**—Patients were on average 66 (SD 7) years old and had a mean systolic blood pressure of



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;  $P=0.0002$ ).

139 (20) mm Hg and a mean diastolic blood pressure of 79 (11) mm Hg.<sup>14</sup> 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**—The total number of strokes, the number of fatal strokes, and the number of non-fatal strokes were all lower in the ramipril group than in the placebo group (table 1). 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;  $P=0.0004$ ). Because of clear benefit, the study was terminated early on 22 March 1999.

**Outcome by type of stroke**—Fewer patients in the ramipril group than in the placebo group had an ischaemic stroke, a haemorrhagic stroke, or a stroke of uncertain origin (table 1).

**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 (tables 1 and 2).

**Results by baseline blood pressure and in other subgroups**—The beneficial treatment effects were consistently seen regardless of baseline blood pressure and in all the subgroups examined (drugs used and presence or absence of previous stroke, coronary artery disease, peripheral arterial disease, diabetes, or hypertension).

**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)
<b>Subtype of stroke</b>			
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.

## 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 addition to blood pressure lowering, by which they could prevent atherosclerotic events.<sup>10</sup> 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.<sup>15</sup> Furthermore, a recent analysis of the United Kingdom prospective diabetes study (UKPDS) showed that the benefits seen with an angiotensin converting enzyme inhibitor (and  $\beta$  blocker) were substantially larger than predicted from differences in blood pressure alone.<sup>16</sup>

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.

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.<sup>17, 18</sup> 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.

**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.

### 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

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## Relation between burden of disease and randomised evidence in sub-Saharan Africa: survey of research

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### Abstract

**Objective** To evaluate whether the amount of randomised clinical research on various medical conditions is related to the burden of disease and health needs of the local populations in sub-Saharan Africa.

**Design** Construction and analysis of comprehensive database of randomised controlled trials in sub-Saharan Africa based on Medline, the Cochrane Controlled Trials Register, and several African databases.

**Setting** Sub-Saharan Africa.

**Main outcome measures** Number of trials and randomised subjects for each category of disease in the global burden of disease taxonomy; ratios of disability adjusted life years (DALYs) per amount of randomised evidence.

**Results** 1179 eligible randomised controlled trials were identified. The number of trials published each year increased over time. Almost half of the trials (n = 565) had been done in South Africa. There was relatively good correlation between the estimated burden of disease at year 2000 and the number of trials performed ( $r = 0.53$ ,  $P = 0.024$ ) and the number of participants randomised ( $r = 0.68$ ,  $P = 0.002$ ). However, some conditions—for example, injuries (over 20 000 DALYs per patient ever randomised)—were more neglected than others.

**Conclusion** Despite recent improvements, few clinical trials are done in sub-Saharan Africa. Clinical research in this part of the world should focus more evenly on the major contributors to burden of disease.

### Introduction

Demand is increasing for research to be prioritised according to the importance of health issues,<sup>1</sup> and burden of disease measures have been proposed to aid this process.<sup>2</sup> There is concern that little medical research is done on diseases affecting people in developing countries.<sup>3</sup> Sub-Saharan Africa is a developing area facing severe, pressing, and often unique health challenges.<sup>4</sup> Its burden of disease per million people is estimated to be five times higher than that of established market economies.<sup>2</sup>

Effective interventions are needed to improve health, and efficacy is best assessed by randomised controlled trials. Randomised controlled trials in Africa have not been comprehensively assessed, and it is not known whether the trials cover the local health needs. We therefore constructed a comprehensive database of randomised controlled trials conducted in sub-Saharan Africa over the past 50 years. We then evaluated whether the amount of randomised evidence relates to the burden of different health problems and whether specific conditions are neglected.

### Methods

#### Eligibility criteria

We considered all randomised controlled trials conducted in sub-Saharan Africa that investigated one or more health problems.<sup>2</sup> We excluded non-randomised and pseudorandomised controlled trials; trials enrolling non-local populations (such as tourists); and trials not in humans. Studies in northern Africa<sup>2</sup> and meeting abstracts, books, and other reports were also excluded.

#### Identification of trials

We searched sequentially Medline (to February 2000), the Cochrane Controlled Trials Register (issue 2, 2000), and the African Published Trials Register of the South African Cochrane Center. The African register has been developed and continuously updated over the past three years from seven diverse international and African databases plus hand searching of back years from 12 major African journals. Terms reflecting randomised controlled trials were conjugated with “Africa,” “sub-Saharan Africa,” and specific geographical names.

#### Database

From each article, we extracted the following information: author, journal, year of publication, unit of randomisation (individual or cluster), sample size, disease(s) targeted (and taxonomy in the *Global Burden of Disease*<sup>2</sup>), type of intervention (therapeutic or preventive), and country or countries of recruitment.

#### Analyses

Descriptive analyses include the geographical distribution of trials, number of new trials published, and esti-