

## THERAPEUTIC INTERVENTIONS

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### INTRODUCTION

Blood pressure is the single most important modifiable risk factor for stroke. Key epidemiological data about the relationship between blood pressure and stroke come from both prospective observational (cohort) studies and randomised controlled trials. Cohort studies provide information about the effects of prolonged blood pressure differences between groups of people (MacMahon *et al.* 1990), while clinical trials provide evidence about the effects of short-term reductions in blood pressure (Collins *et al.* 1990). Cohort studies in both Western (Prospective Studies Collaboration 1995) and Eastern (Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998; Asia Pacific Cohort Studies Collaboration 1999) populations have established a strong and direct association between the risk of first-ever stroke and level of blood pressure, with no detectable lower level of blood pressure below which the risk of stroke does not continue to decline (Fig. 1). A similar association is evident among patients who have had a stroke or transient ischaemic attack (TIA) (Rodgers *et al.* 1996). Thus, blood pressure predicts stroke recurrence as well as stroke occurrence (Fig. 2).

Most of the data on the effects of blood pressure lowering therapy come from trials of the primary prevention of stroke, confirming beyond doubt the benefits of treatment with a wide variety of agents in preventing first-ever stroke in mainly middle-aged men and women with and without 'hypertension'. Moreover, the relative reductions in primary stroke rates of 35–40% in response to reductions of 10–12 mmHg in systolic blood pressure (SBP) and 5–6 mmHg in diastolic blood pressure (DBP) are very much in line with predictions based on the observational epidemiological studies.

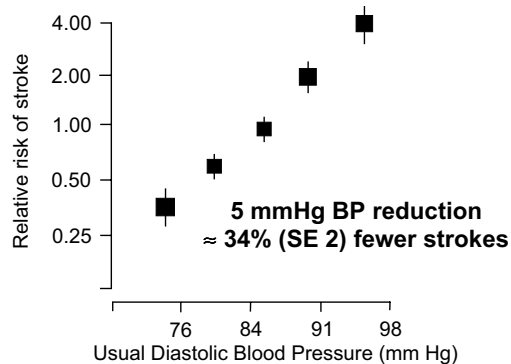
An outstanding issue has, until recently, been whether it is also beneficial to lower blood pressure *after* the onset of stroke to improve long-term outcome and prevent recurrent stroke, and indeed other serious vascular events such as myocardial infarction (i.e. secondary prevention). In addition, whether the benefits of treatment apply across important patient subgroups, such as in those with 'normal' or lower levels of blood pressure after a stroke. These questions are particularly pertinent to reducing the global burden of stroke. According to the World Health Organization Global Burden of Disease study (Murray & Lopez 1996), stroke was the second most common cause of death (4.4 million or 8.7% of deaths) after ischaemic heart disease (6.3 million or 12.5% of deaths), and the sixth most common cause of premature death and disability in 1990. However, stroke is predicted to rank fourth in terms of global disease burden by 2020 because stroke rates rise steeply with age and the world population is ageing rapidly, and adverse lifestyles are being adopted in developing countries. Because individuals with a history of stroke or TIA are at very high risk of recurrent stroke and other vascular events, and because three-quarters of all strokes occur in individuals with 'normal levels' of blood pressure, even modest reductions in blood pressure from widely applicable treatments could confer major absolute benefits on the incidence of stroke and other cardiovascular events. This paper reviews the evidence of the effectiveness of blood pressure lowering for the secondary prevention of stroke in the light of recent data from randomised trials, in particular the results of the Perindopril Protection against Recurrent Stroke Study (PROGRESS) trial (PROGRESS Collaborative Group 2001).

# Long-term management blood pressure

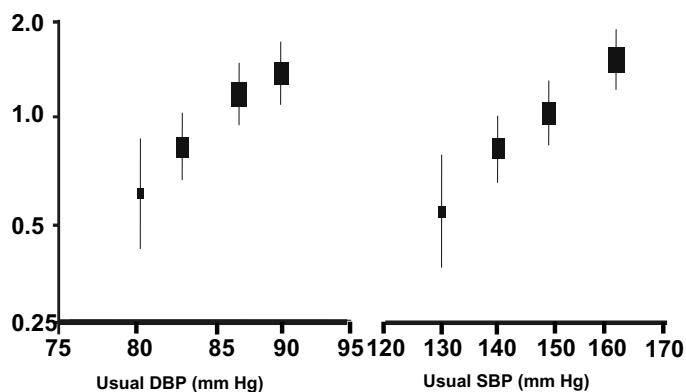


# ment of **re after stroke**

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**Figure 1** Blood pressure and primary stroke



**Figure 2** Blood pressure and secondary stroke. DBP, diastolic blood pressure; SBP, systolic blood pressure

### The effectiveness of blood pressure lowering therapy after stroke

The most reliable evidence for the effectiveness and safety of blood pressure lowering therapy comes from systematic reviews of randomised trials, mainly trials of diuretics and/or beta-blockers against placebo (MacMahon & Rodgers 1993; Blood Pressure Lowering Treatment Trialists' Collaboration 2000; Mulrow 2002). Treatment reduces the risk of stroke by 30–40%. However, most of these trials excluded patients with a history of stroke, so the benefits of blood pressure lowering therapy in this patient group was uncertain. Although meta-analysis of the few trials undertaken in patients with cerebrovascular disease have shown similar risk reductions of about one third (Gueyffier *et al.* 1997; Rodgers *et al.* 1997), these and other data have not been compelling enough to influence clinical practice. Consequently, the approach to blood pressure in the setting of stroke has been rather conservative among neurologists, with far more attention been focused on antithrombotic therapy and carotid surgery.

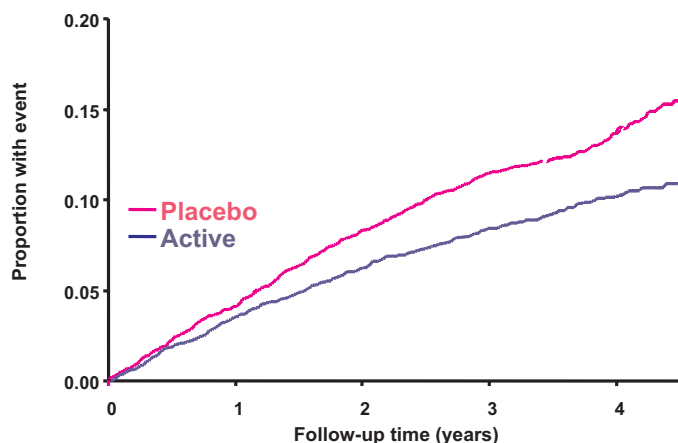
The PROGRESS trial was undertaken in over 6100 individuals from 172 collaborating centres in 10 countries (Australia and New Zealand, China, France and Belgium, Italy, Japan, Sweden,

and the United Kingdom and Ireland) during 1995–2001. The aim was to determine reliably the balance of benefits and risks of a perindopril (an angiotensin-converting enzyme [ACE] inhibitor) blood pressure lowering regimen on recurrent stroke in patients with a history of stroke or TIA. There were no pre-specified blood pressure entry criteria, with the inclusion of both 'hypertensive' and 'non-hypertensive' patients. Potentially eligible patients were enrolled when neurologically stable and they underwent an initial 4 week pre-randomization run-in period during which they received an up-titration of perindopril. Only the patients who adhered to, and tolerated, the run-in treatment were then randomly assigned, on a double-blind basis, to continued active therapy or matching placebo. Active therapy comprised a flexible regimen based on perindopril (4 mg daily), with the addition of the diuretic, indapamide, to maintain control of blood pressure at the discretion of the treating physician.

PROGRESS used a simple pragmatic design in order to include a broad selection of patients and to reflect as much as possible the management of patients in routine clinical practice. Although the average age of patients (60 years; range 26–91 years; 67% over the age of 60) was lower than that of the typical patient with stroke in Western countries, the profile of stroke and blood pressure, and the wide range of socio-demographic, clinical and other characteristics of participants provides strengths to the generalisability of the results.

Overall, blood pressure [systolic blood pressure/diastolic blood pressure (SBP/DBP)] was reduced by an average of 9.0/4.0 mmHg among patients assigned active treatment compared with those assigned placebo. Blood pressure reduction among those treated with combination therapy [12.3/5.0 mmHg (SE 0.5/0.3)] was about double in those in the perindopril-alone group (4.9/2.8 mmHg). For the primary trial outcome, stroke affected 10% of those in the active group (307 patients) compared to 14% in the placebo group (420 patients), which corresponded to a highly significant relative risk reduction in recurrent stroke of 28% (95% CI 17 to 38%;  $P < 0.0001$ ). As shown in Fig. 3, stroke rates between the two groups diverged early and continued for the duration of the trial, indicating an early and persistent effect of treatment. Relative reduction in stroke rates from combination therapy (43%; 95% CI 30 to 54%) was greater than that for single therapy (5%;



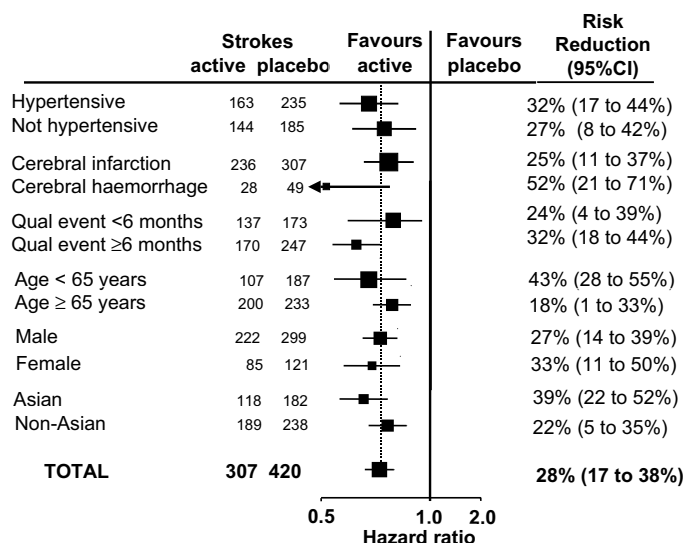


**Figure 3** Effects on stroke events: PROGRESS

95% CI 19 to 23%). However, the confidence intervals around these estimates are wide and overlapping.

An important aspect of PROGRESS was confirmation of the broad benefits of therapy in high risk patients, as also shown in the Heart Protection Prevention Evaluation (HOPE) trial (Heart Outcomes Prevention Evaluation Study Investigators 2000) in which another ACE inhibitor (ramipril; Servier, France) was evaluated in 9297 patients with vascular disease (mainly coronary artery disease) or diabetes with an additional vascular risk factor. In HOPE, the relative risk of stroke was reduced by 32% (156 vs. 226 events) in the ramipril group compared to the placebo group, with the benefits consistent across baseline blood pressures, concurrent treatments, and characteristics of patients (Bosch *et al.* 2002). Similarly, PROGRESS showed that the benefits of treatment were consistent across important subgroups, in particular those characterised by hypertension status (positive vs. negative history or baseline criteria of hypertension), stroke type (ischaemic vs. haemorrhagic stroke at entry), ethnicity (Asian vs. non-Asian patients), and time from stroke onset (early vs. late after a cerebrovascular event) (Fig. 4).

**PROGRESS showed that the benefits of treatment were consistent across important subgroups**



**Figure 4** Effects of treatment by major subgroups: PROGRESS

**CLINICAL IMPLICATIONS OF CURRENT EVIDENCE**

PROGRESS and HOPE resolve some of the clinical uncertainty surrounding blood pressure lowering in patients with stroke. Several important questions can now be more or less answered.

**How important is blood pressure lowering after the onset of stroke?**

The data suggest that the benefits of blood pressure lowering therapy in patients with stroke are substantial. PROGRESS confirms the meta-analyses of cohort studies, and trials in both the primary and secondary prevention of stroke, in showing that a net blood pressure reduction of 9/4 mmHg is associated with about a 30% reduction in the risk of recurrent stroke. Moreover, the benefits of treatment are consistent across all levels of blood pressure, in those

with and without a history of hypertension, and across both ischaemic and haemorrhagic types of stroke. The results suggest that the one stroke could be prevented among every 23 patients treated for 5 years (about 1% per year) and one major vascular event prevented among every 18 patients treated for 5 years. Even greater absolute benefits appear likely with combination therapy, and from treatment among Asian populations where there is a much higher incidence of stroke, and in particular intracerebral haemorrhage, and a steeper association between stroke risk and blood pressure.

#### **How safe is blood pressure lowering after stroke?**

It is well recognised that blood pressure lowering therapy is associated with postural hypotension (5–30% of individuals), with consequent risk of syncope, falls and injury, particularly in older and frail people. Other problems that are more likely to occur with ACE inhibitors are hyponatraemia and renal impairment. These adverse effects are most likely to occur soon after initiating therapy, with the introduction of other medication, particularly non-steroidal anti-inflammatory drugs, and during episodes of illness or dehydration that lower intravascular volume and renal perfusion. Of course, the interpretation about the safety of blood pressure lowering therapy in PROGRESS must be tempered by consideration of the selective nature of the trial study population and the influence of the one month pre-randomization run-in phase. Run-in phases are commonly used in long-term prevention trials to maximise adherence to allocated treatment after randomization and so maximise the efficiency of assessing treatment effects. A drawback to this procedure, however, is that the assessment of the benefits and risks of chronic therapy pertain only to those patients who tolerate therapy acutely, and are willing and able to adhere to follow up.

It is well recognised that blood pressure lowering therapy is associated with postural hypotension, with consequent risk of syncope, falls and injury, particularly in older and frail people

At the end of the run-in phase in PROGRESS, 14% of potential patients were ineligible or had withdrawn from the trial, due mainly to dizziness or hypotension (3.4%), cough (2.7%), and other suspected intolerance (2.3%). There was also one case of non-fatal angio-oedema during this run-in phase. Among those randomised, 22% of patients had prematurely discontinued all medication [active 714 (23%), placebo 636 (21%);  $P = 0.02$ ], or had died, by the end of follow-up. Although the frequency of hypotension that resulted in discontinuation of therapy in the active group was over double that in the control group, the proportion of patients affected was very small, being only 2.2% and 0.9% of the active and placebo groups, respectively. Other reasons for discontinuation included the participant's decision (active 7.6%, placebo 8.2%), and heart failure requiring treatment with an ACE inhibitor or diuretic (active 2.2%, placebo 2.3%). There were three cases of angio-oedema in patients treated with perindopril (0.06%), but none of them were fatal or required intubation.

This high level of adherence to the treatment, together with the low numbers of adverse events documented over several years, reinforces the long-term safety of blood pressure lowering therapy in patients with stroke. In practice, therefore, clinicians should feel confident that their efforts to lower blood pressure with an ACE inhibitor in combination with a diuretic, is safe and effective in patients with stroke, *albeit once a patient has tolerated well the initial introduction of such therapy*. Of course, PROGRESS cannot provide guidance on the speed and degree of blood pressure reduction in this patient group. Pragmatically, however, clinicians should tailor the initiation and monitoring of blood pressure lowering therapy according to age and other relevant characteristics of individual patients.

### How much should blood pressure be reduced?

There has been controversy about how far blood pressure levels should be lowered, and at what point lowering blood pressure is no longer beneficial, and even possibly harmful. Much of the debate about a potential J-shaped (i.e. risk increases at very low pressures as well as with high pressure) rather than linear association of blood pressure and outcome has focused on coronary disease events rather than stroke (D'Agostino *et al.* 1991; Kannel *et al.* 1997). Proponents of the J-curve claim that this association indicates that if blood pressure is lowered too far then blood flow is compromised, leading to ischaemia (Farnett *et al.* 1991; Cruickshank 1992). It is more likely, though, that any apparent J-curve relationship is the result of the inclusion in studies of patients with poor health, which accounts for both a lower pressure as well as a greater likelihood of death from coronary heart disease. This hypothesis is supported by data from the MRFIT study which demonstrate that a J-curve association was only apparent in the first few years of follow-up, and changed to a positive linear relationship thereafter (Flack *et al.* 1995).

Data from clinical trials are particularly relevant to this debate because they provide the most reliable evidence about the effects of blood pressure lowering. In this regard, there has been no evidence of a J-curve association in trials of patients with left ventricular dysfunction (Pfeffer 1993), or elderly hypertensive patients (Hansson *et al.* 1999). In the HOPE trial, beneficial effects of blood pressure lowering were consistent, regardless of baseline blood pressure, even in those with very low baseline pressures (DBP 79 mmHg and SBP 129 mmHg) (Bosch *et al.* 2002). Subsequent analyses of the PROGRESS database demonstrate independent significant reductions in stroke risk across a wide range of blood pressure levels [initial SBP  $\geq$  160, 140–159, or  $<$  140 (mean 128 mmHg) and DBP  $\geq$  95, 85–94,  $<$  85 (mean 77 mmHg)]. Thus, clinicians (and patients) should be reassured that stroke risk can be reduced safely even among those with 'normal' levels of blood pressure after stroke.

### How soon after stroke should blood pressure be lowered?

PROGRESS, HOPE and other trials all recruited patients weeks, or even months, after their vascular event. Therefore, the issue of when to

start blood pressure lowering therapy remains unresolved. Increased levels of blood pressure occur in most patients with acute stroke, and higher levels are associated with increased risk of recurrent stroke and poor outcome (Leonardi-Bee *et al.* 2002). However, acute lowering of blood pressure is a very controversial area and needs further clarification, as some studies, particularly those involving calcium antagonists, have been shown this can be harmful. Although some guidelines recommend treatment above particular levels of blood pressure, it should be recognised that these are all arbitrary and not supported by randomised evidence. Thus, pragmatically, most clinicians wait for several days or more after a major stroke to start treatment at a time when the patients are considered clinically stable, generally when they are beginning to walk again.

### Do the benefits of blood pressure lowering apply to normotensive patients?

In the HOPE trial, a large beneficial effect was demonstrated in those patients with so-called 'normal' levels of blood pressure at entry (DBP 70 mmHg and SBP 120 mmHg). In PROGRESS, the mean blood pressure of all participants at the first visit was 147/86 mmHg, and 48% were classified as 'hypertensive' (mean 159/94 mmHg) and the remainder 'non-hypertensive' (mean 136/79 mmHg). The results show a significant reduction in stroke risk for both patient groups, and on top of concurrent blood pressure lowering treatments and other therapy. Whatever the treatment regimen, the important message to clinicians is that lowering blood pressure following stroke should be considered in *all* patients with stroke, irrespective of their baseline blood pressure level (Fig. 4).

### Should therapy be an ACE inhibitor alone, or an ACE inhibitor and diuretic?

The principal aim of PROGRESS was to assess the effects of a *flexible* ACE inhibitor-based (perindopril; Servier) blood pressure lowering regimen for the prevention of recurrent stroke. Although combination therapy was encouraged, it was at the discretion of investigators to add indapamide (Servier) as study treatment for an individual patient. In the end, almost two thirds of patients were on combination therapy, which reduced blood pressure by 12/5 mmHg and was associated with a stroke risk reduction of about

30%. In contrast, perindopril alone therapy reduced blood pressure by only 5/3 mmHg, and this was associated with a non-significant effect on the risk of stroke. It is important to note, however, that the trial was not designed (and nor powered) to examine the differential effects of combination vs. monotherapy on stroke. The confidence intervals were wide around the point estimate for the treatment effect on stroke resulting from single therapy, so the results could still be consistent with a moderate treatment effect. Moreover, the patient groups differed in other characteristics due to the non-randomised allocation of mono vs. combination therapy. Clearly, combination and single-drug therapy represent differences in therapeutic efficacy, which was reflected in the difference in blood pressure reductions achieved. Previous randomised trials suggest that more intensive blood pressure lowering may confer greater reductions in stroke risk. Thus, the data are not necessarily consistent with an absence of benefit of perindopril, but they do support, in general, an approach of aggressive blood pressure lowering in patients with stroke.

Although there is no definitive evidence that ACE inhibitors are superior in terms of long-term efficacy and safety to other blood pressure lowering agents such as calcium channel blockers, diuretics or beta-blockers (Blood Pressure Lowering Treatment Trialists' Collaboration 2000), PROGRESS and other recent trials have raised important issues about additional benefits independent of blood pressure reduction and through modifications to the renin-angiotensin system. For example, can the additional benefits of combination therapy in PROGRESS be explained by greater blood pressure reduction alone, or are there additional benefits of combination therapy (for example, a 'class effect' of the drugs used)? Certainly, the greater effects of treatment than expected from the size of the blood pressure reductions (3 mmHg SBP and 1 mmHg DBP) in HOPE supports the hypothesis that the benefits of ACE inhibitors are the result of mechanisms over and above blood pressure reduction. The relative benefits of any particular blood pressure lowering agent over another, and the merits of different therapeutic combinations, will only be resolved with more trial data. In the meantime, though, the evidence is strong for using an ACE inhibitor-based blood pressure regime in all groups of patients at high risk of vascular disease, and with the direct evidence in favour of the combination of perin-

dopril and indapamide in those patients with stroke.

## SUMMARY

PROGRESS has provided crucial information on the prevention of vascular disease through the effective management of blood pressure among patients with symptomatic cerebrovascular disease. Clinicians should now consider blood pressure lowering therapy as pivotal to the prevention of stroke in patients who have had a stroke or TIA (and among those at high risk of cardiovascular disease, in general) irrespective of blood pressure levels, and as soon as the patients are clinically stable. Although the choice of therapy will depend on the degree of acceptance of direct evidence, as well as on regulations, prescribing patterns and no doubt costs, the evidence is strong for therapy that maximises the degree of blood pressure reduction using a combination of perindopril and indapamide. Moreover, effective implementation of such therapy in high risk groups in combination with population wide blood pressure lowering strategies, provides arguably the most powerful way of controlling the looming global epidemic of vascular diseases.

## EDITOR'S COMMENT

Both Craig Anderson and I were on the management committee of PROGRESS. Therefore, on the one hand we might over-defend the results, on the other hand we have had to think about them a very great deal. Unlike so many trials in 'neurology', PROGRESS was initiated, designed, organised, analysed and written up by independent (of the sponsors) academic investigators. The data are owned by the University of Auckland. Servier, who make perindopril and indapamide, were bold enough to fund the study and then leave it to the investigators to get on and do it, without interfering. For this they deserve a lot of credit.

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