

Keywords:
blood pressure,
recurrent stroke,
PROGRESS

Blood pressure and stroke; the PROGRESS trial

Feng J He, Graham A MacGregor

Blood Pressure Unit,
St. George's Hospital
Medical School,
London

Correspondence to:
Dr Feng J He
Blood Pressure Unit,
St. George's Hospital
Medical School,
Cranmer Terrace,
London,
SW17 0RE,
UK
Tel: +44 20 8725 2989
Fax: +44 20 8725 2959
E-mail: g.macgregor@
sghms.ac.uk

Accepted for
publication
31st August 2001

JRAAS 2001;2:153-5

All of the treatment trials in high blood pressure (BP) have shown major reductions in the number of people developing strokes,¹ and this reduction for a given BP appears to be equivalent to the epidemiological risk of that elevation in BP,² a remarkable achievement, if true, as the risk of stroke is reversed in a very few years of treatment. However, all these studies have been primary prevention studies and there has, until now, remained some controversy over whether the long-term lowering of BP following a stroke carries similar benefits. It was therefore with great anticipation that the results of the PROGRESS study (Perindopril Protection Against Recurrent Stroke Study),³ were presented at the European Society of Hypertension Meeting in Milan in June 2001. The results clearly demonstrated a major benefit in stroke reduction by lowering BP in people with a previous history of stroke or transient ischaemic attack (TIA). Importantly, this benefit was throughout the range of BP; in other words both normotensive and hypertensive individuals who had suffered a stroke or TIA benefited from BP-lowering.

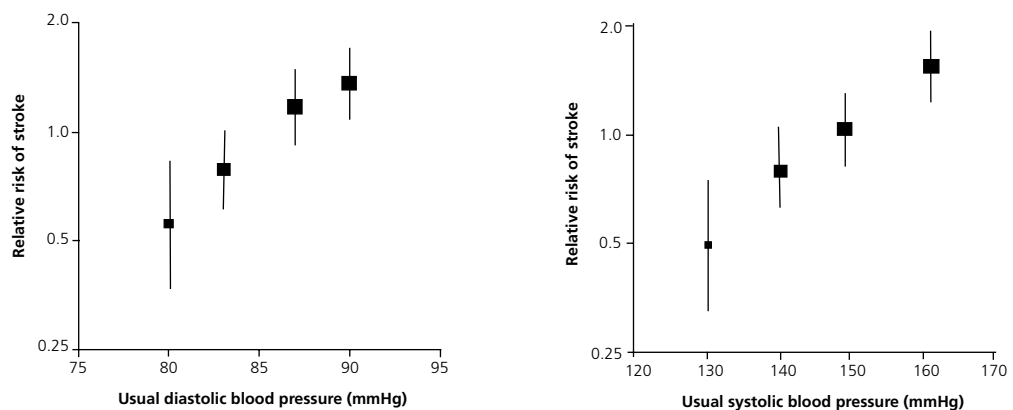
Increasing BP is the most important contributory factor to primary stroke. Epidemiological studies show a continuous and graded relationship between BP and the risk of primary stroke, and there is no evidence of any lower BP threshold, below which further reductions in BP have no effect on stroke risk.² Treatment trials have now

clearly demonstrated that a prolonged reduction in BP of 10-12/5-6 mmHg for just a few years reduces the incidence of primary stroke by 35-40%.¹ This is very similar to those predicted from the observational epidemiological studies.

Accumulating evidence suggests that there is a similar relationship between BP and secondary (or recurrent) stroke as that of primary stroke. Analysis of the data from the UK-TIA aspirin trial, which involved 2435 individuals with a history of TIA or minor stroke followed up for four years, showed that BP level was an important determinant of recurrent stroke, not only in hypertensive, but also in normotensive individuals.⁴ Indeed, there was a direct and continuous relationship between the usual levels of BP and subsequent risk of recurrent stroke (Figure 1).⁴ This relationship was independent of age, sex, smoking history and aspirin use.

Some supportive evidence on the role of BP in the secondary prevention of stroke comes from treatment trials. A recent meta-analysis of nine randomised, controlled trials in 6752 patients with prior stroke or TIA showed that BP-lowering treatments reduced the incidence of recurrent stroke by 28%.⁵ However, in this meta-analysis, one study, the PATS (Post-stroke Antihypertensive Treatment Study),⁶ accounted for 75% of the individuals entered into the meta-analysis. The results, therefore, of the meta-analysis were essentially representative of the PATS results. PATS was a ran-

Figure 1 Continuous relationship between usual blood pressure and the risk of stroke in 2435 individuals with a history of transient ischaemic attack (TIA) or minor stroke during 4 years' follow-up in the UK-TIA aspirin trial.



Reproduced with permission from A Rogers. *BMJ* 1996;313:147.

**Journal of
the Renin-
Angiotensin-
Aldosterone
System**
(Including other
peptidergic systems)

September 2001
Volume 2
Number 3

domised, double-blind, placebo-controlled trial, in which 5665 Chinese patients who had a history of stroke or TIA were randomised to either indapamide treatment or placebo. After two years of treatment with indapamide, BP was reduced by 5/2 mmHg and the risk of recurrent stroke reduced by 29%.⁶ However, it has remained controversial as to whether high BP following a stroke should be treated, and in particular whether BPs within the normal range following a stroke should also be lowered.

The PROGRESS study was conducted in 172 hospitals in Australia, Belgium, China, France, Japan, Italy, New Zealand, Sweden and the United Kingdom. Eligible patients were treated with 2 mg perindopril daily for an initial period of two weeks followed by 4 mg perindopril daily for two weeks, irrespective of their starting BP level. If perindopril was tolerated, patients were then entered into a double-blind study comparing perindopril (4 mg daily) with the option of indapamide (2.5 mg daily, in Japan 2 mg daily) with matching placebos.⁷ A total of 6105 participants completed the study.

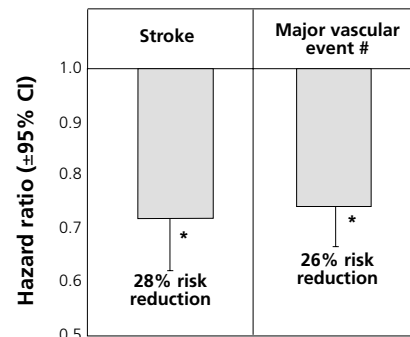
After an average of 4.2 years follow-up, BP was 9/4 mmHg lower in subjects receiving active treatment compared with those on placebo. There was a progressively increasing difference between the active treatment and placebo group in the number of recurrent strokes and major vascular events (including stroke, heart attack or death from cardiovascular disease). On average, the active lowering of BP decreased the risk of recurrent stroke by 28% (95% CI: 17%–38%, $p < 0.0001$) and major vascular events by 26% (95% CI: 16%–33%, $p < 0.0001$) (Figure 2). Importantly, the reductions in recurrent stroke that occurred were similar in the normotensive and hypertensive individuals.

Further analysis of the trial showed that the combination of perindopril and indapamide caused a larger and more significant reduction in recurrent stroke (43% risk reduction) and major vascular events (40% risk reduction), with a fall in BP of 12/5 mmHg, compared with the perindopril alone group, in which there was only a small fall in BP (5/3 mmHg) and no significant reduction in the risk of recurrent stroke and vascular events. However, the numbers in the perindopril monotherapy group were small and from the evidence presented so far, it is difficult to draw any clear conclusions, except that a greater fall in BP is related to a greater reduction in the risk of recurrent stroke and vascular events.

The design of the PROGRESS study,⁷ starting an angiotensin-converting enzyme (ACE) inhibitor first and ensuring it was tolerated, meant that there appeared to be few dropouts during the trial. What remains unclear is how far the reduction in stroke risk is due to the lowering of BP *per se*. There is already some evidence^{8,9} to suggest that ACE inhibitors (ACE-I) may protect the vasculature independently of BP-lowering, for example following myocardial infarction in the HOPE study (Heart Outcomes Prevention Evaluation),⁹ although the possible contribution of BP reduction to the outcomes in this study remains controversial.

Figure 2 Average reduction in the risk of stroke and major vascular events in all participants (n=6105) during 4.2 years' follow-up in the PROGRESS study with active treatment (perindopril ± indapamide) compared with placebo.

PROGRESS All participants (n=6105)



* $p < 0.0001$ active treatments vs. placebo.

major vascular events include stroke, heart attack or death from cardiovascular disease.

In the primary prevention of stroke, the recent overviews of the outcome trials indicate that it is the BP fall that largely accounts for the outcome and that the different classes of antihypertensive drugs, ACE-I, calcium antagonists, diuretics and beta-blockers seem to confer a similar overall cardiovascular benefit,¹⁰ although far larger numbers would be needed to show significant differences between treatments. However, there have been suggestions that ACE-I may offer more cardio-protection and calcium antagonists more protection against stroke,^{10,11} although these are extremely speculative.

One area of BP and stroke management which remains controversial is when antihypertensive treatment should be started following stroke. In the first few days following a stroke, cerebral autoregulatory mechanisms are deranged and BP-lowering may lead to cerebral hypoperfusion. In the PROGRESS study, treatment was not started until patients had stabilised after an acute stroke.⁷ Ongoing trials looking at the acute effects of BP reduction following a stroke are in progress.

Epidemiologically, there is a very clear and direct relationship between salt intake and stroke,¹² and an inverse relationship between potassium, and thereby the consumption of fruit and vegetables, and stroke.¹³⁻¹⁷ Worldwide, much more effort should be put into reducing salt intake and increasing fruit and vegetable consumption, since this will reduce BP¹⁸⁻²¹ and thereby stroke incidence. This is particularly important as the majority of primary strokes that are attributable to BP occur in the upper range of 'normal' BP. Furthermore, both a reduction in salt and an increase in fruit and vegetable consumption appear to have independent effects on reducing strokes in addition to the effect of the fall in BP.^{22,23} The recent DASH-Sodium Study (Dietary Approaches to Stop Hypertension)²¹ shows that the combination of reducing salt and increasing fruit and vegetable consumption has large

effects on lowering BP similar to, or greater than, that seen with a diuretic in both hypertensive and normotensive individuals.

In conclusion, the PROGRESS study clearly demonstrates that lowering BP with a combination of an ACE-I (perindopril) and diuretic (indapamide) causes a major reduction in recurrent stroke, and also other cardiovascular complications, and importantly shows equal benefits in both hypertensive and normotensive subjects following a stroke. Whilst there will be questions as to exactly what therapy should be used and how far BP should be lowered, all patients who have had a stroke or TIA should now be considered for BP reduction, irrespective of their starting level of BP. The PROGRESS study demonstrates that the combination of a diuretic with an ACE-I causes major reductions in subsequent cardiovascular complications in these individuals.

References

1. MacMahon S, Rodgers A. Blood pressure, antihypertensive treatment and stroke risk. *J Hypertens* 1994;12 (suppl 10):S5-14.
2. MacMahon S, Peto R, Cutler J *et al*. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in BP: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765-73.
3. PROGRESS Study. <http://www.iih.org/progress/milestones.html>.
4. Rodgers A, MacMahon S, Gamble G, Slattery J, Sandercock P, Warlow C. Blood pressure and risk of stroke in patients with cerebrovascular disease. *BMJ* 1996;313:147.
5. Gueyffier F, Boissel JP, Boutitie F *et al*. The INDANA (Individual Data Analysis of Antihypertensive intervention trials) Project Collaborators. Effect of antihypertensive treatment in patients having already suffered from stroke. Gathering the evidence. *Stroke* 1997;28:2557-62.
6. PATS Collaborating Group. Post-stroke Antihypertensive Treatment Study. A preliminary result. *Chin Med J* 1995;108:710-7.
7. PROGRESS Management Committee. Blood pressure lowering for the secondary prevention of stroke: rationale and design for PROGRESS. *J Hypertens* 1996;14 (suppl 2):S41-S46.
8. Sharpe N. The effects of ACE inhibition on progression of atherosclerosis. *J Cardiovasc Pharmacol* 1993;22 (suppl 9):S9-12.
9. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145-53.
10. Staessen JA, Wang JG, Thijs L. Cardiovascular risk and blood pressure reduction: an overview of the outcome trials (Abstract). *J Hypertens* 2001;19 (suppl 2):S145.
11. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibition, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000;356:1955-64.
12. Perry IJ, Beevers DG. Salt intake and stroke: a possible direct effect. *J Human Hypertens* 1992;6:23-5.
13. Khaw KT, and Barrett-Connor E. Dietary potassium and stroke-associated mortality. A 12-year prospective population study. *N Engl J Med* 1987;316:235-40.
14. Ascherio A, Rimm EB, Hernan MA *et al*. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation* 1998;98:1198-204.
15. Iso H, Stampfer MJ, Manson JE *et al*. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. *Stroke* 1999;30:1772-9.
16. Gillman MW, Cupples LA, Gagnon D *et al*. Protective effect of fruits and vegetables on development of stroke in men. *JAMA* 1995;273:1113-7.
17. Josphipura KJ, Ascherio A, Manson JE *et al*. Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA* 1999;282:1233-9.
18. MacGregor G. Nutrition and blood pressure. *Nutr Metab Cardiovasc Dis* 1999;9 (suppl):6-15.
19. Appel LJ, Moore TJ, Obarzanek E *et al*. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997;336:1117-24.
20. Siani A, Strazzullo P, Giacco A, Pacioni D, Celentano E, Mancini M. Increasing the dietary potassium intake reduces the need for antihypertensive medication. *Ann Intern Med* 1991;115:753-9.
21. Sacks FM, Svetkey LR, Vollmer WM *et al*. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N Engl J Med* 2001;344:3-10.
22. Antonios TF, MacGregor GA. Salt—more adverse effects. *Lancet* 1996;348:250-1.
23. He FJ, MacGregor GA. Beneficial effects of potassium. *BMJ* 2001;323:497-501.