PROGRESS in the secondary prevention of stroke

Over the last 10 years there has been considerable progress in the development of secondary prevention strategies for ischaemic stroke. No longer is aspirin the cornerstone of stroke secondary prevention. Trials like ESPS-2[1] and CAPRIE,[2] have established the place of antiplatelet agents in secondary prevention. The 4S[3] and CARE[4] studies, among others, and the recently presented Heart Protection Study[5] have alluded to the benefits of statins, not only in the setting of ischaemic heart disease, but now also in the setting of cerebrovascular disease. Until the publication of the PROGRESS study[6] in September of last year, the question of blood pressure reduction in the setting of secondary prevention was unanswered and contentious.

As long as 30 years ago, two trials (the Carter trial[7] and the Hypertension-Stroke Co-operative Study Group trial[8]) were specifically designed to address this issue. The results were consistent with a beneficial effect from lowering blood pressure on stroke recurrence in hypertensive patients, but they did not reach statistical significance. More recently, the INDANA collaborators[9] summarised all of the randomised controlled trials on the effects of blood pressure-lowering drugs in survivors of stroke or transient ischaemic attack (TIA). They showed a significant benefit in reducing the risk of stroke recurrence by 30% from treatment.

This finding was mainly based on the results of the PATS trial.[10] Published in 1995 in preliminary form only, the PATS study included 5,665 Chinese patients and showed considerable benefits in treating survivors of stroke or TIA with the thiazide-like diuretic, indapamide. Unlike earlier trials, this study alluded to benefits in treating blood pressure after stroke, irrespective of initial blood pressure, but was confounded by the design. PATS required usual antihypertensive treatment to be withheld and so may have misleadingly shown benefit.

The PROGRESS study

The PROGRESS study was a large, randomised, controlled trial designed to determine the effects of angiotensin-converting enzyme (ACE) inhibitor-based (perindopril 4 mg and indapamide 2.5 mg) blood pressure lowering on the risks of stroke and other major cardiovascular events. Eligible patients had a prior history of stroke (infarction or haemorrhage) or TIA with no indication for or contraindication to treatment with an ACE inhibitor. There was no prespecified blood pressure entry criterion and continuation of usual blood pressure treatment was encouraged.

Overall, treatment with the perindopril-based therapy reduced total stroke by 28% and total major vascular events by 26%. Combination therapy was more impressive than monotherapy with a 43% reduction in total stroke and 40% reduction in major vascular events compared to a 5% reduction in total stroke and 4% reduction in major vascular events using perindopril alone. There were particularly large reductions in recurrent cerebral haemorrhages (50%) and in non-fatal myocardial infarction (38%). There were also reductions in hospital admissions and dementia. The greater effects of combination therapy on stroke risk suggest that the additional blood pressure reduction achieved with more than one agent conferred important additional benefits. Moreover, the same favourable outcomes were apparent for both normotensive (< 140 mmHg/85 mmHg) and hypertensive (> 160 mmHg/95 mmHg) stroke patients.

In view of the large number of patients who experience TIA or stroke, this study has important clinical implications. Combination therapy over five years treatment prevented one fatal or major non-fatal event among every 11 patients treated. The figure was one in 18 for monotherapy. These reductions are of the same magnitude as that of antiplatelet agents in secondary prevention of ischaemic stroke, but apply regardless of stroke subtype.

Secondary prevention

When should secondary prevention be optimised? Antiplatelet agents have proven value within the first 48 hours after ischaemic stroke but lowering blood pressure within the first 72 hours of acute stroke is controversial and can lead to dramatic neurological deterioration.[11] Our policy is to withhold antihypertensive treatment for 72 hours in the acute setting and then cautiously add antihypertensive agents thereafter. Ideally, the PROGRESS drugs should be added when the patient is clinically stable with regards to their neurological and cardiovascular status. In practice, this usually means one to two weeks after the acute event. There should also be no contraindication for ACE or diuretic therapy. The aim is to reduce blood pressure without causing side effects, such as orthostatic hypotension (especially in the elderly) or deterioration in renal function from underlying renovascular

disease. It may also be sensible to monitor blood pressure and renal function on a couple of occasions during initiation. The PROGRESS drugs should be added into established treatment, not substituted for it. As the majority of patients will be seen in a community or out-patient setting, it is important to minimise adverse effects. First-dose hypotension is a well recognised complication of ACE inhibition. Perindopril was chosen for PROGRESS on account of its gradual onset of action, its long half-life, allowing once-daily dosing, and its reduced tendency to cause first-dose hypotension in high-risk patients. Perindopril lowered blood pressure with sparing of global and regional cerebral perfusion in hypertensive stroke patients with moderately stenosed or occluded carotid arteries.[12]

PROGRESS did not indicate a level to which blood pressure should be lowered. The definition of hypertension used in the trial was a blood pressure of 160/90 mmHg (based on lowest levels adopted in previous trials that showed that antihypertensive treatment regimes reduced the risk of stroke). As benefits of using a perindopril-based blood pressure-lowering regime were equally applicable to those patients previously considered normotensive, then perhaps current definitions of hypertension and normotension may not be applicable to this specific group of patients. Combination therapy reduced stroke risk by more than a third across a wide range of blood pressures, including reductions in risk among individuals in whom initial pressure was substantially less than 140 mmHg systolic or 85 mmHg diastolic; indeed, average initial blood pressure in the lowest tertile was approximately 125/75 mmHg. Given that almost half of the patients in PROGRESS had a diastolic blood pressure less than 85 mmHg, blood pressure targets set for other groups may be inappropriately high for many patients with cerebrovascular disease. British Hypertension Society guidelines[13] for diabetics should now be our minimum target for stroke patients also. These suggest treating blood pressure that is consistently above 140/80 mmHg, using additional antihypertensives if necessary. For patients who tolerate it, further reduction is likely to be useful.

It is likely that it is blood pressure reduction which confers protective effects against stroke and other cardiovascular events, rather than unique properties of the PROGRESS drugs. The observed overall reduction (28%) in stroke risk is in agreement with results of other trials using beta blockers or diuretics in which diastolic blood pressure was reduced by 5 or 6 mmHg.[14] Combination therapy lowered blood pressure to a greater extent and offered greater cardiovascular protective effects than monotherapy with ACE inhibition alone.

Evidence suggests that high-risk vascular patients benefit from ACE inhibitor therapy.[15] A high proportion of the stroke population have clinically overt ischaemic heart disease and peripheral vascular disease; many are also diabetic. Studies suggest that a sizeable proportion have latent but significant atheromatous disease. As well as its antihypertensive effects, ACE inhibitor treatment protects against cardiovascular morbidity and mortality by a number of mechanisms.[16] The choice of agent should also be influenced by tolerability and safety issues – both PROGRESS and HOPE[15] used a long-acting ACE inhibitor and, in the PROGRESS trial, a remarkable 87% of patients were still taking their treatment after four years, vindicating the choice of drugs.

Conclusion

Approximately 5% of referrals seen by our stroke service and 8% of patients discharged from the care of our stroke service over the last five years are currently maintained on an ACE inhibitor. The majority were established on ACE inhibitors for an indication other than secondary prevention of stroke, such as hypertension or left ventricular systolic dysfunction. The decision to treat blood pressure more aggressively in this patient population was deferred until the results of PROGRESS were known. We now have a duty to offer optimal secondary prevention to patients who would benefit. That includes anyone who has suffered a stroke or TIA within the last five years (though since benefit continued to increase through the four to five years of the PROGRESS study, perhaps time since last stroke is irrelevant). We are thus establishing a clinic to review these patients with regard to recent trial results.

Editors' note

This is the eighth article in our stroke series. Previous articles have included:

- Cerebrovascular disease (editorial) (*Br J Cardiol* 2001; **8**:482)
- The epidemiology of stroke (*Br J Cardiol* 2001;**8**:507-13)
- The pathophysiology of stroke (*Br J Cardiol* 2001;**8**:586-9)
- Acute management of stroke (*Br J Cardiol* 2001;**8**:654-7)
- Prevention of vascular disease following acute ischaemic stroke (*Br J Cardiol* 2001;**8**:704-11)
- Stroke rehabilitation (*Br J Cardiol* 2002;**9**:23-30)
- Prognosis, outcome and recurrence of stroke (*Br J Cardiol* 2002;**9**:103-105)

A ninth article looking at 'Stroke in the patient with coronary heart disease' can be found on pages 163–7 in this issue.

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