Interventions to lower blood pressure in secondary stroke prevention

Control of treatable vascular risk factors is the mainstay of secondary prevention of stroke, hypertension being the most prevalent. A linear association between increasing blood pressure (BP) levels post-stroke and poor outcome has been demonstrated across the range of BP values commonly encountered. Drs Amit Mistri and Martin Fotherby summarise the evidence regarding blood pressure lowering as a secondary prevention measure.

Stroke is the third most common cause of mortality in the UK and the single most common cause of severe disability. The National Audit Office, in November 2005\(^1\) highlighted the need for an emergency response to acute stroke, improved access to rehabilitation and support services, and emphasis on primary and secondary prevention measures. With an estimated annual cost of £7bn to the UK, and a new stroke occurring every five minutes in the UK, the burden to patients, carers and society alike is substantial. The societal cost from strokes is 1.5 times that for the expenses for coronary artery disease, which explains the increasing attention towards the management of cerebrovascular disease.

Pharmacological treatment of acute stroke to improve outcome has been disappointing. Thrombolysis is restricted to the first three hours following a stroke, and therefore applicable to only a small proportion of patients at present. Also there has been little success with trials studying neuroprotective agents. Early antiplatelet therapy is associated with significant benefit, although in absolute terms, this benefit is small\(^2\). Therefore, initial supportive treatment, followed by rehabilitation and secondary prevention by controlling known risk factors, is the management plan for most patients.

Relationship between BP and stroke

In patients with no prior history of cerebrovascular disease, the linear association between increasing blood pressure (BP) levels and first stroke has been demonstrated convincingly, with the risk of cardiovascular events doubling for every 20mmHg SBP (systolic blood pressure) or 10mmHg DBP (diastolic blood pressure) rise across the range of BP values from 115/75 to 185/115mmHg\(^3\). When considering recurrent stroke (beyond the early
post-stroke phase), a similar association between achieved BP and stroke incidence was noted across the range of achieved BP (112/72–168/102mmHg), in a post hoc analysis of patients in the PROGRESS study. Also a retrospective analysis of 2,201 patients in the UK-TIA study showed a strong positive linear relationship between usual BP and stroke risk (hazard ratio more than doubled per 20mmHg rise in SBP and 10mmHg rise in DBP).

A ‘J’-shaped relationship has been demonstrated between post-stroke DBP and stroke recurrence, with the nadir at 80–84mmHg. There was no association with other BP parameters. The results are difficult to interpret with 69 per cent of patients receiving antihypertensive therapy, and the possibility of co-morbid conditions associated with low BP (eg, myocardial infarction) influencing it. It is reassuring that the Leigh Valley Recurrent Stroke Study did not reproduce the possible J-shaped association between BP and stroke recurrence. Those with lowest follow-up DBP (<80mmHg) had a reduced risk of recurrent stroke compared to those with DBP80–89mmHg (RR0.4, p=0.02). Higher SBP (≥140mmHg) was associated with relative risk (RR)2.4 compared to SBP<140mmHg for stroke recurrence. This reinforces the linearity of the association demonstrated in the PROGRESS and UK-TIA studies.

Also, in patients with cerebrovascular disease high SBP (≥140mmHg) is an independent predictor of risk of intracerebral haemorrhage (hazard ratio 2.17, compared to patients with SBP<140mmHg). The risk of stroke increases with BP in the majority of patients with carotid artery disease, who therefore should be offered antihypertensive therapy. However, in those with bilateral carotid stenosis >70 per cent, this association is reversed. Aggressive BP reduction would not be advisable for this uncommon group of patients and a carotid revascularisation procedure may be appropriate prior to initiation of antihypertensive therapy. There is no evidence to guide the management of BP in those patients not fit for revascularisation.

**Intervention studies**

Metaanalyses of trials studying antihypertensive therapy as a secondary prevention intervention have shown a significant reduction in recurrent stroke and vascular events (odds ratio for all stroke: 0.72–0.76, cumulative vascular events: 0.77–0.79). The data has clearly been influenced by the results of more recent large studies with adequate power to detect differences in outcome – PATS, PROGRESS and HOPE.

**How soon after stroke should we start BP treatment?**

There is little evidence currently to support or refute early BP lowering intervention (before the first one to two weeks), and this is therefore not advised, except in compelling situations (sustained extreme BP elevation, co-existent heart failure, aortic dissection, acute myocardial infarction, acute renal failure or as part of guidelines for thrombolysis in early acute ischaemic stroke). In the ACCESS study candesartan given <72 hours of ischaemic stroke vs > seven days in 342 patients with BP >180/105mmHg resulted in a significant 47.5 per cent reduction in the secondary outcome of all-cause, cerebral and cardiovascular mortality in the acute candesartan treatment arm, but with no effect on the primary outcome of death and disability at three months. However, this was a small study in a select group of stroke patients. There is good evidence of the benefits of BP lowering beyond the early post-stroke phase.

In neurologically stable patients, initiation of BP lowering therapy can be considered approximately one to two weeks after the onset of stroke. Furthermore, there may be benefit in commencing antihypertensive therapy prior to discharge from hospital to improve compliance. In patients having had a transient ischemic attack (TIA), therapy can be started soon after the event.

**At what level of BP should treatment be initiated?**

Because of the high overall cardiovascular risk in patients with cerebrovascular disease, hypertensives as well as ‘normotensives’ are likely to benefit from BP reduction. Supporting this recommendation, the PROGRESS study showed patients with any BP level benefited from treatment. In the subgroup classified as non-hypertensive at baseline, BP was lowered from a mean of 136/79mmHg to 128/75mmHg with significant relative reduction in stroke (27 per cent) and major vascular events (24 per cent). Therefore patients with SBP >130 should be offered antihypertensive therapy for reduction of future risk of vascular events.

The applicability of this recommendation to...
groups that have not been included in the clinical trials (eg, the very elderly and frail) is uncertain, and a pragmatic approach will be required to estimate the risk/benefit ratio (risk = likelihood of side effects of aggressive BP lowering, especially in normotensives, benefit = reduction of subsequent vascular events), until direct evidence is available.

What is the recommended BP target?
The National Clinical Guidelines for stroke recommend a target BP of 140/85mmHg, with further reduction employing a PROGRESS-type regime. The recently published British Hypertension Society Guidelines (http://www.bhsoc.org/pdfs/BHS_IV_Guidelines.pdf) and the Joint British Societies guidelines – JBS2 (http://bhf.org.uk/professionals/uploaded/january2006.pdf) guidelines suggest a lower target BP of 130/80mmHg, as for all patients with hypertensive target organ disease. The American Heart Association guidelines mention uncertainty with regards to the absolute BP reduction or target value, and note that benefit has been associated with an average BP reduction of ~10/5mmHg in persons with or without a history of hypertension. A blood pressure target of 130/80mmHg for hypertensives and a BP reduction of 10/5mmHg for normotensives is recommended, if tolerated. It is well documented that cerebral autoregulation is impaired following stroke; however, whether this persists over a longer period is uncertain. There is thus a theoretical possibility that BP reduction may result in reduced cerebral blood flow and its consequences. This explains some clinicians’ reluctance with regards to BP reduction in patients with cerebrovascular disease. However, no detrimental effects were observed in the subgroup with the lowest achieved BP (SBP<120) in PROGRESS – accepting the bias inherent in post hoc analysis.

What agents should be used?
If there is a compelling indication for early BP lowering, agents that should be avoided include sublingual nifedipine (rapid BP lowering can exacerbate cerebral ischaemia), oral beta-blockers and high dose intravenous nimodipine, a dihydropyridine calcium channel blocker (worse outcome compared to placebo in randomised trials). Preliminary evidence suggests that ACE inhibitors or ARBs may be the preferred agents, as they shift the cerebral autoregulation curve to the left, and BP lowering can be achieved without significant reduction in cerebral blood flow. Beyond the acute phase, BP lowering drugs associated with significant benefit in placebo-controlled secondary stroke prevention trials are summarised in Table 1. It would be reasonable to choose drugs that are cheap and have been associated with significant benefit in clinical trials of relevant patients. Thiazide-type diuretics and ACE inhibitors are recommended first-line agents. Further options include ARBs and dihydropyridine CCBs. Other antihypertensives may be preferred if they may be beneficial for co-morbidities (eg, beta-blockers for IHD).

Are clinical guidelines followed?
All primary and secondary stroke prevention measures are underused. Specifically, attainment of BP targets in the guidelines is seen only in the minority. The reasons for this are multifactorial, including:

> patient factors (poor utilisation of preventive therapies in general as opposed to curative therapy; lack of awareness of risk; denial;

| Table 1. Agents studied in secondary stroke prevention trials: effect on outcome and BP |
|---------------------------------|---------------------------------|------------------|-------|
|                                   | Odds ratio – stroke (95% CI) | Odds ratio – vascular events (95% CI) | BP reduction (mmHg) | Trial       |
| Indapamide                        | 0.71 (0.58-0.88)              | 0.77 (0.63-0.94)              | 5/2               | PATS        |
| Perindopril + indapamide          | 0.55 (0.45-0.68)              | 0.58 (0.48-0.69)              | 12/5              | PROGRESS    |
| Ramipril                          | 0.85 (0.56-1.30)              |                                 | 3/2               | HOPE subgroup |
Occurrence of an index stroke or TIA should prompt a systematic assessment for identification of vascular risk factors, patient education, plans for initiation of preventive intervention, goal setting and regular monitoring of the effectiveness of individual interventions. Patient empowerment and clarity in terms of leadership and responsibility for the individual management steps is paramount, and more needs to be done to bring clinical practice in line with the existing evidence-base.

Conflict of interest: Dr Mistri is the Trial Coordinator for the CHHIPS Study, an acute post-stroke BP intervention study. Dr Fotherby has none declared.

Key points

- Beyond the acute post-stroke phase (~first two weeks), BP lowering is the most important intervention in secondary stroke prevention.
- BP lowering should be considered in all patients with SBP>~130 mmHg, with the aim of reducing BP by 10/5 or down to 130/80mmHg, whichever is lower.
- BP reduction with thiazide-like diuretics, ACEI-thiazide combination and ACEI alone has been shown to result in significant benefit.
- The majority of patients with cerebrovascular disease do not achieve BP levels recommended by guidelines.
- Systematic assessment for vascular risk factors should be carried out following a stroke or TIA, with plans for initiating preventive intervention and monitoring clinical effectiveness of therapies put in place.

References

1. National Audit Office. DoH Reducing Brain Damage: Faster access to better stroke care. 1-60. 16-11-2005
13. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 19,113 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358(9287):1003-1014