Control of Blood Pressure After Stroke

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Editorial Commentary

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A cornerstone of primary stroke prevention is built on treating "hypertension" in asymptomatic subjects who are usually at low or medium vascular risk, dogma based on the results of numerous randomized, controlled trials and meta-analyses of them. Similarly, several trials have shown that blood pressure (BP) should be lowered in patients who have had a recent stroke.[1–3] Note here the distinction between treating hypertension in primary prevention and lowering BP in secondary prevention.

Three randomized trials were of sufficient size to help determine clinical practice in patients with cerebrovascular disease. The Post-stroke Antihypertensive Treatment Study (PATS) found that treatment with the thiazide-like diuretic, indapamide, reduced BP (by 5/2 mm Hg) and stroke recurrence by 29% in 5665 Chinese patients.[1] In contrast, the Heart Outcomes Prevention Evaluation (HOPE) Study was a trial of ramipril (angiotensin converting enzyme inhibitor [ACE-I]) in 9297 patients with high vascular risk in which 1013 patients had a history of previous stroke. Within this subgroup, ramipril was effective at reducing BP (by 11/4 mm Hg) whereas the composite outcome of stroke, myocardial infarction (MI), and vascular death was reduced by 30%. The largest trial to date was the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS), which assessed a treatment regime based on another ACE-I, perindopril, given with or without indapamide (at the investigators choice) in 6105 patients with previous ischemic stroke or primary intracerebral hemorrhage.[3] Overall, active treatment was associated with a relative risk reduction (RRR) in stroke of 28%; however, combined treatment (perindopril+indapamide) was far more effective in reducing both BP (12/5 mm Hg) and stroke (RRR 43%) than perindopril alone (BP difference, 5/3 mm Hg; stroke RRR 5%, nonsignificant). Notably, treatment was particularly effective in patients of Asian origin and in preventing recurrence in those whose index event was a cerebral hemorrhage (rather than infarct).[3]

A meta-analysis of these trials and 4 earlier smaller ones reported that antihypertensive therapy was effective in reducing recurrent stroke (odds ratio [OR], 0.76), MI (OR, 0.79), and vascular events (OR, 0.79).[4] Heterogeneity between drug classes was apparent: β-receptor antagonists did not seem to reduce any vascular events, diuretics alone reduced stroke but not MI, and ACE-I reduced MI but not stroke. However, the most effective intervention was dual therapy, which reduced each of the 3 outcomes (Figure 1).[4] More recently, the relatively small Morbidity and Mortality After Stroke–Eprosartan Versus Nitrendipine for Secondary Prevention (MOSES) Trial reported that eprosartan (angiotensin receptor antagonist) was more effective than nitrendipine (calcium channel blocker [CCB]) in preventing stroke recurrence,[5] a result that is difficult to interpret, because the effectiveness of CCBs in patients with previous stroke is unknown. A much larger trial, Prevention Regimen For Effectively avoiding Second Stroke (PRoFESS, n=20 000) is underway, which is assessing the effect of telmisartan (angiotensin receptor antagonist) on stroke recurrence in patients with ischemic stroke.

These data strongly support the routine use of antihypertensive agents in patients with previous ischemic stroke. And yet, the article published in this edition of the journal from the North East MElbourne Stroke Incidence Study (NEMESIS) by Paul and Thrift[6] is depressing, suggesting that many patients out in the community are hypertensive some 5 years after their event and, indeed, 5 years after the publication of PROGRESS. Paul and Thrift[6] found that 82% of their patients had hypertension that was uncontrolled (BP >140/90 mm Hg) in more than one third of patients. Although most were receiving some antihypertensive medication, a small group (6%) of patients were unaware that their BP was elevated suggesting, perhaps, that they were not receiving active primary care follow-up. It is well known that many patients out of the environment of trials cease to take long-term medication; for example, ≈30% of those with essential hypertension have ceased therapy by 12 months[7]; hence, it is vital that patients with previous stroke have long-term follow-up in the community to motivate compliance. Perhaps unsurprisingly, persistence with therapy seems to be higher with newer agents (such as ACE-I).[7]

It is increasingly clear that most patients need ≥2 drugs to control their BP, as seen in trials such as HOPE and PROGRESS.[2,3] NEMESIS found that most patients (65%) were on monotherapy,[6] which will explain, in part, the lack of BP control. Interestingly, the most common drug class for monotherapy was ACE-I, perhaps reflecting that both PROGRESS and NEMESIS arose from Australia, although this observation is also in keeping with a recent US study demonstrating a large increase in use of ACE-I.[8] Dual therapy may also be inadequate for controlling BP, especially if inappropriate drug combinations are used. For example, combining an ACE-I and β-receptor antagonist (2 classes that suppress the renin system), as was done in 4% of NEMESIS patients, is unlikely to lead to synergistic effects, especially in older people[9] who tend to have low renin levels anyway. This combination was associated with uncontrolled hypertension. Another inappropriate combination is use of a CCB and diuretic. In contrast, the most common dual therapy combination associated with adequate BP control in NEMESIS involved an ACE-I and diuretic,[6] drugs that have

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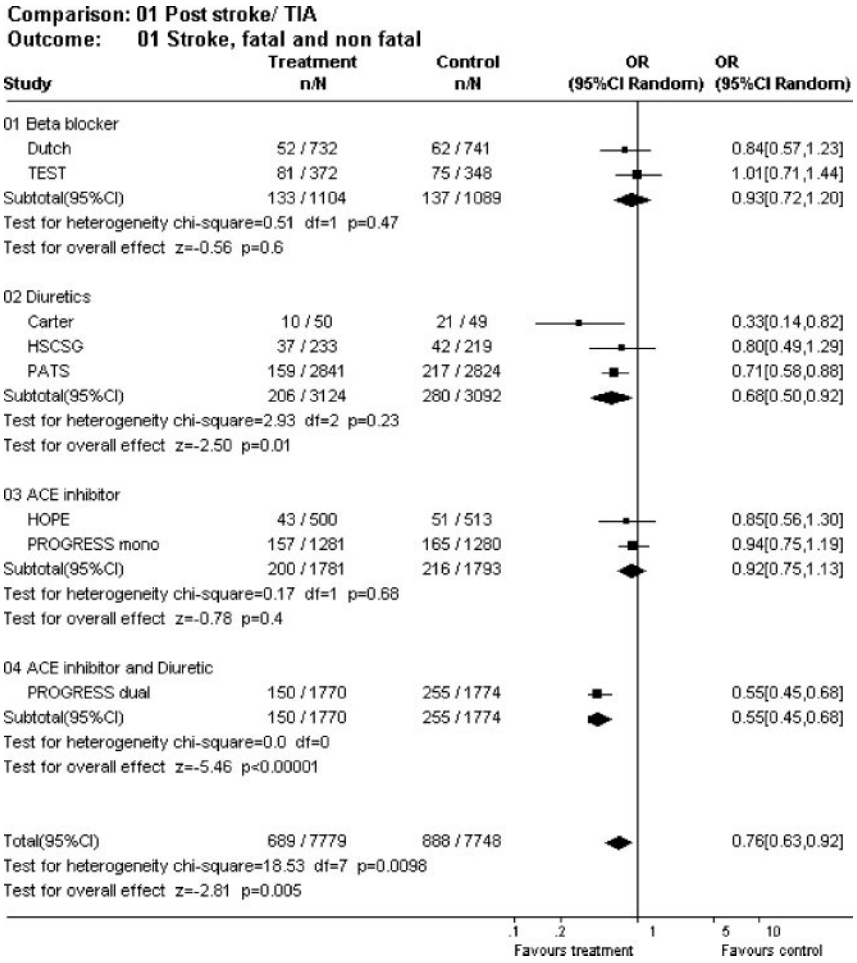

Forrest plot of the effects of antihypertensive therapy in patients with previous stroke or transient ischemic attack on subsequent stroke (fatal and nonfatal). Reprinted with permission from Reference 4.

opposing effects on the renin system. The use of optimal combinations of antihypertensive agents is now recommended in national guidelines.[10] In addition to lack of awareness and poor compliance, therapeutic inertia (the failure of health care providers to increase treatment when therapy goals are unmet) accounts for a large proportion of uncontrolled hypertension.[7,11] BP control is lowest in those patients whose providers have high inertia, whereas patients of providers with low inertia have an increased number of medications and better control.

Elevated BP is a potent modifiable risk factor for stroke, whereas many patients who have has a previous stroke are hypertensive afterward. Lowering BP is an effective method for reducing the risk of subsequent stroke and it is beholden on all of those who look after stroke patients, whether general practitioners, stroke physicians, or neurologists, to ensure that BP control is achieved. Most patients will need ≥2 drugs, and combinations should be logical and based on class pharmacological activities, especially taking account of effects on the renin system.

Disclosures

P.M.W.B. was an investigator in PROGRESS and is a local investigator and member of the steering committee for PRoFESS. N.S. reported no conflicts.

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