Q J Med 1999; **92**:63–66

Editorial

QJM

What should we do about blood pressure and stroke?

As we draw towards the end of this millennium, it will become clear whether the aspirations raised by the Health of the Nation document will be realized with regard to the reduction in mortality from stroke. The target of a 40% decrease in stroke deaths by the year 2000 in those aged 65–74 years may initially have appeared optimistic without any specific new interventions, but mortality rates have been consistently falling in both the UK and most, but not all, Westernized countries over the past 2–3 decades.[1] This decrease in mortality is probably due to a combination of decreased stroke incidence and stroke severity, as well as a reduction in death rate following the acute event. However, in the UK there are still over 120 000 strokes per annum, about 20% being due to a recurrence. Overall, 20% will die within the first few months of the event, and up to 35% of the survivors will still be dependent after a year.[2] Primary stroke reduction must come from attacking the major risk factors, of which hypertension remains the primary treatable cause. This editorial deals primarily with the relation between ischaemic stroke and blood pressure (BP), and the benefits or otherwise of BP reduction in both primary and secondary prevention.

Data from prospective observational studies have highlighted the strong association between increasing BP levels and stroke incidence for both cerebral haemorrhage and infarction. In the Prospective Studies Collaboration, a meta-analysis of 45 studies involving 450 000 subjects aged 15–99 years with a mean follow-up of 16 years, diastolic blood pressure (DBP) levels were closely related to stroke risk after adjustment for other potential confounding variables; for every 10 mmHg DBP increase, stroke risk rose by 80%.[3] However the BP/stroke relation varies with age, the gradient being much steeper in younger than in older age groups. In the Honolulu heart study, the relative risk (RR) of thromboembolic stroke associated with hypertension in 45–54-year-old males was 6.1 compared with 1.6 in the 65–81-year-olds.[4] The attributable stroke risk due to hypertension similarly decreases with age, with $<20\%$ of strokes in the $\geqslant 65$ years age group being related to elevated BP levels, compared to 50% in 45–54 year olds.[4] So despite the majority of strokes occurring in the elderly population, and hypertension remaining a significant risk factor in this age group, other factors become increasingly more important in older people. It has been estimated that for the population as a whole, 75% of strokes occur in the 90% of individuals with a BP $<155/95$ mmHg.[5] Hypertension type also affects stroke risk. In older age groups, isolated systolic hypertension (ISH) has a greater RR than diastolic hypertension (3.2 and 2.1 respectively) when compared to normotensives, but this increased risk with ISH is reversed in those aged 40–59 years (7.7 and 10.3, respectively).[6]

There has been much debate as to whether the relation between increasing BP levels and stroke is linear or J-shaped, particularly in older groups. MacMahon *et al.*[7] have convincingly demonstrated a log-linear correlation between cerebrovascular disease risk and BP in younger age groups, and more recent studies have shown that the same holds true for the $\geqslant 65$ years age group.[8,9] The apparent J-shaped curve seen in some studies is probably related to co-morbidity at the time of BP measurement rather than from low BP *per se*. The relation between BP and cardiovascular disease in the very elderly ($\geqslant 75$ years) is not as obvious as in younger age groups, and an increasing body of evidence suggests that high levels may actually indicate a favourable survival pattern.[10] If it is unclear that hypertension in this very elderly group is a risk factor, it is even more uncertain as to the benefits of treatment, and hopefully studies such as Hypertension in the Very Elderly Trial (HYVET) will answer this important question.[11]

Evidence continues to accumulate from intervention studies in both young and elderly hypertensives of the benefits from pharmacological BP lowering. Reducing levels by about 15/6 mmHg in younger patients will decrease stroke incidence by nearly 50%, but this would only account for about 1–2 strokes avoided per 1000 patient-years of treatment.[12] In older patients, for similar BP decreases, stroke risk will be reduced by about 34%, cardiovascular deaths by 23% and the overall death rate by 10%, which

means a reduction of up to 9 strokes per 1000 patient-years of treatment (allowing for withdrawal biases) in older hypertensives.[12] Patients with both combined hypertension (systolic and diastolic) and ISH appear to benefit from treatment to the same degree.[13,14] The most common first-line anti-hypertensive agents to date have been diuretics and beta-blockers, but more recently the longer-acting dihydropyridine calcium channel blockers have also been shown to reduce stroke incidence.[14] Only when we have the results of ongoing studies comparing the older and newer families of anti-hypertensive agents will we know whether the more recently introduced compounds provide any additional benefit. However, if we seriously wish to reduce stroke incidence, it is insufficient just to diagnose hypertension and start treatment if good BP control is not achieved. The level of BP on treatment is a far better predictor of stroke incidence than pre-treatment BP values.[15]

As to the optimal BP level on treatment to reduce stroke risk in hypertensives the recently published Hypertension Optimal Treatment (HOT) study suggests the lowest risk is achieved at a SBP of 140–145 mmHg and a DBP of $\leqslant$80 mmHg.[16] What most studies have failed to do is to assess the effects of treatment on the different stroke subtypes, and it is unlikely that all will benefit to the same degree from BP lowering.

Casual BP levels are elevated during the first 24 h post ictus (over 80% of acute stroke patients will have a BP $>$160/90 during initial post stroke phase) and fall spontaneously in the subsequent 10–14 days.[17] Because cerebral autoregulation is impaired after the acute event, cerebral blood flow is very sensitive to changes in systemic BP levels. It might be reasoned that initially high values after cerebral infarction would be of benefit in terms of increasing blood flow to the ischaemic penumbra. Conversely, sustained rises could be detrimental by increasing the risk of cerebral oedema and the possibility of haemorrhagic transformation of the infarct. The mechanisms underlying the rise in BP post stroke are probably due to a combination of many factors including impairment of baroreceptor sensitivity,[18] increased sympathetic nervous system activity,[19] activation of the renin aldosterone mechanisms, the Cushing reflex and importantly, the alerting response to BP measurement in these patients.[20] Observational studies reporting outcome in relation to initial BP levels have been markedly at variance, some showing an improved prognosis in those with high BP levels,[21] others showing the exact opposite,[22] while some have shown no relation to outcome at all.[23] There are many reasons for this disparity in terms of study methodology, but a recently published large, prospective study overcame many of these problems using 24-h BP monitoring. This showed, even allowing for other known risk factors of a poor stroke outcome, that for every 10 mmHg increase in 24-h SBP levels on admission, the likelihood of death or severe disability at 30 days is almost doubled.[24] However, this does not necessarily mean that lowering BP will be of benefit in the acute post-stroke period and the literature is littered with reports of adverse effects of pharmacological reduction in the acute situation. It is even theoretically possible that increasing BP in the acute stroke period may be of benefit, perhaps in those with significant carotid stenosis.[25] To date there have been no large, randomized trials of BP modification in the acute stroke period, and these are much needed. Currently there seems little evidence to suggest that pharmacologically altering BP acutely is of value, unless there are other pressing medical reasons, e.g. hypertensive encephalopathy, at least in the first 1–2 weeks after cerebral infarction.

As almost 50% of stroke survivors will have elevated BP levels 6 months or more after the acute event, it is not surprising that anti-hypertensive treatment in the post-stroke period is frequently advocated.[26] Although raised BP levels are a strong risk factor for primary stroke, the relation with stroke recurrence is nowhere near as clear. Meissner *et al.*[27] in one of the biggest studies to date found BP control was unrelated to accumulative stroke recurrence rates over a 10-year follow-up period. Other workers have found hypertension post stroke a risk factor, with recurrence rates in hypertensives of 16% over 2 years compared with 12% in normotensives.[28] More recently, Rogers *et al.*,[29] using data from the UK TIA study, showed a near linear relation between follow-up SBP and DBP levels and relative risk of stroke, a 5 mmHg lowering of DBP theoretically being associated with a 30% reduction in stroke recurrence, although the BP range was narrow at 130–160/80–90 mmHg. A meta-analysis of studies reporting the relation between stroke recurrence and post-stroke BP levels has suggested that raised SBP and DBP levels were associated with a RR of stroke recurrence of about 1.7, though the analysis was limited by the number of negative studies which did not report actual rates (Manktelow and Potter, unpublished data). To date, there have been only two randomized intervention studies of the treatment of hypertension post stroke,[30,31] and three further studies that have involved both normotensives and hypertensive TIA and stroke subjects.[32–34] In hypertensives, non-fatal stroke recurrence was not significantly reduced by active treatment, although combined fatal and non-fatal stroke events were reduced by 35% (95% CI 1–57%). Taking all intervention studies including normotensives and hypertensives,[30–34] fatal stroke recurrence was not reduced, but total number of strokes was reduced by 23% (95% CI 10–34%) and all major cardiovascular events by one-fifth

(Manktelow and Potter, unpublished data). However, these results are highly influenced by the PAT (Post-stroke Antihypertensive Treatment) study,[34] as this provided over two-thirds of the patients in these studies, and therefore care must be taken in interpreting the results.

Although it is clear that reducing BP levels is an effective primary preventative measure in reducing stroke, many questions still remain unanswered. Is anti-hypertensive treatment of benefit in the very elderly or following stroke? If so, is the same degree of benefit seen for all stroke subtypes? When after stroke should anti-hypertensive medication be started, at what BP level should treatment be instigated and what is the best anti-hypertensive agent to use in these patients? Hopefully some of these questions will be answered by ongoing studies, but until then, in the acute and post-stroke periods at least, we will have to rely on our clinical judgement with regard to the use of anti-hypertensive medication.

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