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Antihypertensive Therapy in the Prevention of Stroke

What, When and for Whom?

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Abstract

It is clear that antihypertensive regimens based on a low dose thiazide diuretic are effective for the primary prevention of stroke, particularly in older patients. In patients with diabetes mellitus who are at a higher risk of stroke, low dose thiazide diuretics and ACE inhibitors are of benefit. In those with isolated systolic hypertension, long-acting dihydropyridine calcium antagonists, in addition to

low dose thiazide diuretics, have also been shown to significantly reduce stroke risk. However, to attain sufficient lowering of blood pressure (BP) to most effectively reduce the risk of stroke (i.e. to levels of 140-150/80-85mm Hg or lower and perhaps to <140/<80mm Hg in patients with diabetes mellitus) combination therapy will be required. Immediately following stroke BP tends to fall spontaneously and therapy is probably not required in the great majority of patients during the first few days poststroke. If treatment is required shortly after this period, agents with a slow and gentle onset of action appear to be preferable; some preliminary data suggest that ACE inhibitors, despite lowering systemic BP, have no significant effect on cerebral blood flow. However, there is little clinical outcome data to clearly define the role of antihypertensive treatment in the early poststroke period. Whether existing antihypertensive therapy should be continued following stroke is also unclear, but such decisions may be influenced by factors such as the actual BP level, other indications for treatment (e.g. angina pectoris or cardiac failure) or the presence of dysphagia. There is more evidence to suggest that, some weeks to months following stroke (particularly a minor stroke), lower rather than higher BP is favourable, and better control of high BP with therapy reduces stroke recurrence.

Of the many stroke risk factors so far identified, blood pressure (BP) remains one of the most important modifiable influences. Until recently, attention was focused on diastolic BP (DBP) where a direct linear relationship was noted with stroke risk, even within the 'normal' range. Stroke risk increases by 46% for every 7.5mm Hg increase in DBP.[1] The influence of raised systolic BP (SBP), particularly in older individuals, is now appreciated; even in the presence of a 'normal' or low DBP, a high SBP is an important stroke risk factor (see table I). Indeed, pulse pressure (SBP minus DBP), which probably reflects arterial stiffness, may be the best haemodynamic indicator of stroke risk.[2] Other factors related to BP also appear to increase stroke risk, e.g. left ventricular hypertrophy, left atrial size, atrial fibrillation, left ventricular dysfunction and coronary heart disease (CHD) in general. These factors are all potentially modifiable by lowering high BP.[3]

1. Relationship of BP to Stroke Type

Because of the varying pathologies leading to the stroke syndrome, the strength of the association of a particular stroke type with BP may also vary. High BP could contribute to stroke risk through the following mechanisms:[4]

1. Rupture of microaneurysms on small penetrating arteries leading to intracerebral haemorrhage (ICH).

2. Arteriosclerosis and hypertensive lipohyalinosis of the small penetrating arteries leading to lacunar infarction.

3. Atherosclerosis in the extracranial (and less often intracranial) arteries leading to atherothrombotic disease and to arterial embolism.

4. Promotion of CHD, cardiac failure, left ventricular hypertrophy (LVH) and atrial fibrillation leading to cardiogenic embolism.

It has been estimated that hypertension is associated with 70 to 75% of lacunar infarcts and 40 to 50% of atherothrombotic stroke, with possibly a weaker association between hypertension and emboli arising from the heart. The relationship of hypertension to ICH has recently been examined using modern imaging techniques[5] such as computerised tomography and magnetic resonance

Table I. Effect of prolonged differences in systolic blood pressure (SBP) and diastolic blood pressure (DBP) on stroke risk

Reduction in SBP/DBP (mm Hg)	Reduction in stroke risk
9/5	1/3
18/10	1/2

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imaging. Although hypertension remains the most important modifiable risk factor for ICH it may not be as strong a factor as previously reported. A history of hypertension approximately doubled the risk of ICH, a similar risk to that for ischaemic stroke, however, there was a much stronger association between hypertension and fatal ICH.[5]

2. Mechanisms Through Which High BP Increases Stroke Risk

Haemorrhage as a direct consequence of high arterial pressure appears straightforward and is consistent with the lower risk of ICH following reduction of high BP. However, complications of hypertension, including the majority of strokes, are atherothrombotic in nature rather than haemorrhagic. This apparent paradox is understandable by considering the effect of high BP on abnormalities of vessel wall, blood flow and its constituents – Virchow's triad of factors promoting thrombosis. Associations between increasing BP and adverse effects on these factors have been reported with regard to, for example, endothelial cell activation/dysfunction, platelet activation, other haemostatic factors and leucocyte adhesion.[6,7] In particular, increasing SBP and pulse pressure have been associated with measures of endothelial cell dysfunction and monocyte adhesion, processes that may be involved in the promotion of thrombosis and atherosclerosis.[8] The effects of lowering high BP on such processes have not been extensively studied, let alone the effects of different antihypertensive treatments.[9]

Further mechanisms by which lowering BP may influence stroke include effects on regression of left ventricular mass. LVH on electrocardiogram and echocardiography has been associated with an increased risk of stroke, both haemorrhagic and atherothrombotic.[10] The LVH may act not only as a marker of prolonged hypertension, but may also predispose to left atrial enlargement, increased risk of atrial fibrillation and, hence, stroke. Regression of LVH occurs with many classes of antihypertensive drugs, most consistently with ACE inhibitors, calcium antagonists and thiazide diuretics, and less so with α-blockers.[11,12] However, whether regression of LVH affects stroke rate and prognosis in general, over and above effects of BP reduction, remains to be determined.

An increase in left atrial size has been associated with the development of atrial fibrillation and stroke and can be reduced with various classes of antihypertensive drugs. Regression of left atrial size has been shown most convincingly with thiazide diuretics, in contrast to smaller changes induced by β-blockers, calcium antagonists, ACE inhibitors and α-blockers.[13]

3. Effect of Antihypertensive Therapy on Primary Stroke Prevention

Overviews of randomised controlled trials of antihypertensive therapy on stroke incidence show that the BP reduction achieved (approximately 11/6mm Hg) confers a 38% reduction in risk of stroke after 2 to 3 years of treatment. The relative risk reduction is similar for middle-aged and elderly patients, and those with mild, moderate or severe hypertension.[1] This reduction represents almost full reversal of the risk associated with long term BP elevation, as suggested from the prospective observational studies,[14] and indicates that antihypertensive treatment prevents stroke directly by acting on precipitating factors rather than solely through reversing atherosclerosis.

3.1 Which Patients Benefit?

Earlier clinical trials showed the benefit of treating moderate to severe hypertension in middle-aged patients. More recent studies have been conducted in patients where stroke is more common, i.e. older patients with mild hypertension.[15-22]

3.1.1 Level of BP

Recent studies confirm that patients with mild diastolic (DBP ≥100mm Hg) and combined systolic-diastolic hypertension (SBP ≥160 and DBP ≥90mm Hg) benefit from antihypertensive therapy. In addition, 3 studies have shown the benefit of treating isolated systolic hypertension (SBP ≥160 and DBP <90 or 95mm Hg): the Systolic Hy-

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pertension in the Elderly Programme (SHEP),[20] Systolic Hypertension in Europe (SYST-Eur)[21] and Systolic Hypertension in China (SYST-China).[22] In the Swedish Trial in Older Patients with hypertension (STOP) study,[15] the majority of patients had only mild elevation of DBP but high SBP; the results emphasised the benefit of treating high SBP (≥160mm Hg) regardless of the level of DBP.

3.1.2 Age

Patients below the age of 60 years have shown a similar relative reduction in stroke risk with antihypertensive therapy to those above 60 years of age. In addition, an overview of outcome data in patients aged >80 years who entered recent trials of antihypertensive drugs suggests that they benefit from therapy with a 34% reduction in stroke, an incidence similar to that seen in younger patients.[23] Initiating antihypertensive therapy in some patients in their early to mid 80s may be appropriate given that benefits may be seen within 2 years.

3.1.3 Patients with Diabetes Mellitus

Compared with patients who do not have diabetes mellitus, those with diabetes mellitus have at least a 2-fold higher risk of stroke and enjoy a similar relative benefit from antihypertensive therapy and hence a higher absolute benefit.[20] Low dose chlorthalidone in the SHEP study[24] reduced the relative risk of cardiovascular events by a similar degree (34%) in patients with or without diabetes mellitus, although strokes were reduced nonsignificantly in patients with diabetes mellitus by 22% [relative risk reduction (RR) 0.78, 95% confidence interval (CI) 0.45 to 1.34]. The wide CIs are probably a result of the smaller number of individuals with diabetes mellitus recruited. In a middle-aged population, the UK Prospective Diabetes Study[25] showed that good BP control (<150/85mm Hg) was associated with a significant 44% reduction in stroke events compared with less tight control (a difference of 10/5mm Hg between groups).

3.1.4 Individuals at High Risk of Stroke and Vascular Disease

Although the relative risk of stroke is similar across a range of patient groups studied, the actual benefit achieved will depend on the individual's prevailing stroke risk. This is most strongly influenced by age, the level of usual SBP, smoking habits and the presence of atrial fibrillation, diabetes mellitus or LVH. Probability of stroke based on these factors can be estimated from the Framingham risk factor equation.[26] For example, a man in his mid-70s with borderline systolic hypertension (SBP 155 to 164mm Hg) and a history of cardiovascular disease will have an estimated 16% 10-year probability of stroke, i.e. 1.6% per annum risk from stroke alone or 3.2% per annum if atrial fibrillation is present. Antihypertensive therapy could reduce the risk of stroke to <1% and 2% per annum, respectively.

Of course, the benefits of antihypertensive therapy are not restricted to stroke reduction but extend to other cardiovascular events including CHD and, in particular, reduction of congestive heart failure (CHF). Therefore, overall cardiovascular risk must be taken into account as well as stroke risk. It has been considered appropriate to start antihypertensive therapy if cardiovascular risks exceed 2% per annum (which can be estimated simply from the New Zealand risk tables[27]). On this basis, most men over 60 years of age and women over 70 years with mild hypertension (e.g. BP 160/95mm Hg) would require treatment. Because stroke and cardiovascular risk is directly related to BP across the normal to high range, some patients with 'high normal' SBP, i.e. 140 to 159mm Hg, may be at sufficient risk to justify treatment. This will include individuals with evidence of cardiovascular disease, target organ damage or those who have a cardiovascular event rate ≥2% per annum. Clearly from the above discussion this will include most men and many women over aged 70 years with SBP >140mm Hg whose cardiovascular event rate will exceed 2% per annum. To provide a balance between reducing stroke and cardiovascular risk and overmedication of the older population, factors such as the following will need to be considered:

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- ensuring 'usual BP' is recorded by taking multiple measurements on several occasions or by using ambulatory BP recording
- taking account of standing BPs if lower than sitting BPs
- the general condition and life expectancy of the patient
- the wishes of the patient
- nondrug or lifestyle changes that can be instituted, at least initially, rather than drug therapy.

That the majority of strokes occur in people aged over 65 years with 'normal' BP emphasises the need for lowering BP across the population, or at least a reduction in the age associated rise in BP. It is very likely that lifestyle changes involving diet and physical exercise with accompanying reductions in the prevalence of being overweight would contribute greatly to this goal.

A summary of BP and age thresholds for considering antihypertensive therapy is shown in table II.

Table II. Who to treat: blood pressure and age thresholds for considering introducing antihypertensive therapy (high risk = cardiovascular event risk ≥2% per annum)

Threshold	Treatment decision
SBP ≥160mm Hg	Yes
SBP 140-159mm Hg	Yes, if high risk including patients with diabetes mellitus or vascular disease (e.g. myocardial infarction, peripheral vascular disease)
DBP ≥90mm Hg	Yes, if >60 years or high risk
Age ≤80 years	Yes
Age >80 years	Yes, if 'biologically fit' (e.g. no known coexisting diseases likely to lead to death within 2 years) and able to comply with and tolerate therapy (e.g. without precipitating symptomatic orthostatic hypotension)

DBP = diastolic blood pressure; **SBP** = systolic blood pressure.

3.2 What Antihypertensive Therapy Should be Used?

Several nondrug therapies or lifestyle approaches have been shown to lower BP in those at most risk of stroke, i.e. older individuals.[28,29] The effect on BP of several of these approaches are detailed in table III. Such approaches can be used on their own in patients with high normal BP or borderline hypertension with low levels of cardiovascular risk or combined with drug therapy in those at higher risk.

Table III. Examples of lifestyle changes shown to reduce blood pressure and their approximate effect in hypertensive patients

Lifestyle changes	Reduction in SBP/DBP (mm Hg)
Bodyweight reduction of 1kg	2/1
Salt reduction of 50 mmol/day	5/3
Increased fruit and vegetable consumptions from 2 to 7 portions a day	7/3
Aerobic exercise daily for approximately 40 min	5/3

DBP = diastolic blood pressure; **SBP** = systolic blood pressure.

Of the several classes of antihypertensive drugs available, most direct evidence for the primary prevention of stroke comes from trials considering the efficacy of thiazide diuretics, β-blockers and calcium antagonists.

3.2.1 Thiazide Diuretics

The recent use of low dose thiazide diuretics, particularly in older patients, has resulted in reductions in the relative risk of stroke, CHF, CHD and total mortality.[30] When results from trials in patients aged >60 years (shown in table IV) were combined, low dose thiazide therapy reduced stroke events by 39%.[31]

3.2.2 β-Blockers

In the Medical Research Council (MRC) elderly trial, Hypertension in Elderly Persons Trial and the STOP study, regimens were based on β-blocker therapy, although in the latter 2 trials >50% of the elderly participants received combined thiazide/β-blocker treatment. Analysis of the effects of β-blockers on stroke and cardiovascular end-points in elderly patients is therefore heavily influenced by the results of the MRC elderly trial which showed no significant reduction in stroke, coronary or all cardiovascular events. The outcome of these trials on stroke and cardiovascular events is shown in table V. These results are balanced by other studies showing benefits of β-blocker–based

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Table IV. Antihypertensive trials using low dose thiazide diuretics in older patients (>60 years): effect on stroke and cardiovascular events

Study	Year	Treatment	FU (years)	n	Reduction in					
					SBP (mm Hg)	DBP (mm Hg)	all stroke (%)	p-value	CV events (%)	p-value
EWPHE[16]	1985	HCTZ 25mg + triamterene	4.5	416	21	7	43	0.15	38	0.023
SHEP[19]	1991	Chlorthalidone 12.5mg	4.5	2365	11	5	38	0.0003	32	<0.05
MRC Elderly[18]	1992	HCTZ 25mg + amiloride 2.5mg	5.8	1081	16	7	31	0.04	35	0.0005

CV = cardiovascular; **DBP** = diastolic blood pressure; **EWPHE** = European Working Party on High blood pressure in the Elderly; **FU** = follow-up; **HCTZ** = hydrochlorothiazide; **MRC** = Medical Research Council; **n** = number of patients receiving active treatment; **SBP** = systolic blood pressure; **SHEP** = Systolic Hypertension in the Elderly Programme.

regimens such that overall β-blockers are estimated to reduce stroke risk by 25 to 29%.[30]

3.2.3 Calcium Antagonists

Three placebo-controlled clinical outcome studies conducted in patients >60 years of age who received long-acting dihydropyridine calcium antagonists have been published. Both SYST-Eur[21] and SYST-China[22] enrolled patients with isolated systolic hypertension, and the Shanghai Trial of Nifedipine in the Elderly (STONE)[32] enrolled patients with combined hypertension (SBP >160mm Hg and DBP >96mm Hg); all studies showed significant relative reductions in stroke events as shown in table VI. However, as the STONE study was single blind with allocation to nifedipine or placebo in an alternate fashion, less weight should be attached to these results compared with results from the other studies which were both double-blind and randomised in design.

3.2.4 Comparison of β-Blockers, Thiazide Diuretics and Dihydropyridine Calcium Antagonists

In patients treated with diuretic-based therapy there is an approximately 13% (nonsignificant) lower stroke risk compared with those using a β-blocker–based regimen.[1] Although there is insufficient evidence to definitely conclude that β-blockers are less effective at reducing stroke risk than thiazide diuretics, in contrast to the effects of thiazides, they did not reduce CHD and total mortality, as illustrated in table VII. The differences between the drugs appears more marked in older than younger patients with hypertension (see table VIII). Many authors and hypertension management committees no longer recommend β-blocker–based therapy as first-line antihypertensive treatment in elderly patients.[31,33] Reasons suggested for the poor performance of β-blockers in older patients include their weak antihypertensive effect which may be related to their adverse haemodynamic profile in elderly patients with hypertension,

Table V. Antihypertensive trials using β-blockers in older patients (>60 years): effect on stroke and cardiovascular events

Study	Year	Treatment	FU (years)	n	Reduction in					
					SBP (mm HG)	DBP (mm Hg)	all stroke (%)	p-value	CV events (%)	p-value
Coope & Warrender[16]a	1986	Atenolol 100mg	4.4	419	16	10	42	0.03	Nil	nd
STOP[15]a	1991	β-Blocker + HCTZ 25mg + amiloride 2-5mg	2	812	19.5	8.1	47	0.008	40	0.003
MRC Elderly[18]	1992	Atenolol 50mg	5.8	1102	14	7	18	ns	4	ns

a Many subjects were taking β-blockers and a thiazide diuretic.

CV = cardiovascular; **DBP** = diastolic blood pressure; **FU** = follow-up; **HCTZ** = hydrochlorothiazide; **MRC** = Medical Research Council; **n** = number of patients receiving active treatment; **nd** = no data available; **ns** = not significant; **SBP** = systolic blood pressure; **STOP** = Swedish Trial in Older Patients with Hypertension.

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Table VI. Antihypertensive trials using dihydropyridine calcium antagonists in older patients (>60 years): effect on stroke and cardiac events

Study	Year	Treatment	FU (years)	n	Reduction in					
					SBP (mm HG)	DBP (mm Hg)	all stroke (%)	p-value	cardiac events (%)	p-value
SYST-Eur[20]	1997	Nitrendipine	2	2398	10.1	4.5	42	0.003	26	0.03
SYST-China[21]	1998	Nitrendipine	3	1253	8.0	3.2	38	0.01	37	0.09
STONE[30]	1996	Nifedipine sustained release	2.5	891	9.3	5.5	57	0.003	60	0.0001

DBP = diastolic blood pressure; **FU** = follow-up; **n** = number of patients receiving active treatment; **SBP** = systolic blood pressure; **STONE** = Shanghai Trial of Nifedipine in the Elderly; **SYST-China** = Systolic Hypertension in China; **SYST-Eur** = Systolic Hypertension in Europe.

i.e. maintenance of increased peripheral resistance along with a low cardiac output. Even after allowance for differences in BP, thiazide diuretics appear to be more effective than β-blockers.[18] However, β-Blockers do remain of benefit following myocardial infarction.[34]

On indirect comparison long-acting dihydropyridine calcium antagonists (table VI) and thiazide diuretics (table IV) appear to have similar efficacy in reducing stroke risk. A comparison of the effects of an intermediate-acting dihydropyridine, isradipine, and hydrochlorothiazide on carotid artery intima media thickness (a surrogate measure of atherosclerosis) reported similar progression in both treatment groups but a higher incidence of major cardiovascular events in those taking the calcium antagonist.[35] Other studies have suggested that short-acting calcium antagonists such as nifedipine may be associated with an increased risk of coronary events.[36] In patients with hypertension who have type 2 diabetes mellitus, preliminary reports suggest ACE inhibitors may prevent more cardiovascular events, particularly myocardial infarction, than dihydropyridine calcium antagonists.[37,38]

Table VII. Summary of overviews comparing trials of thiazide diuretics and β-blockers in patients with hypertension: odds ratios (OR) for cardiovascular (CV) and coronary heart disease (CHD) events and mortality from stroke, CV disease and all causes[31]

	Thiazide diuretics OR (95% CI)	β-Blockers OR (95% CI)
CV event[a]	0.61 (0.51-0.72)	0.75 (0.57-0.98)
Total stroke	0.67 (0.49-0.90)	0.76 (0.48-1.22)
CHD	0.74 (0.64-0.85)	1.01 (0.80-1.29)
CV mortality	0.75 (0.64-0.87)	0.98 (0.78-1.23)
All mortality	0.86 (0.77-0.96)	1.05 (0.88-1.25)

a Fatal and nonfatal strokes and transient ischaemic attack.
CI = confidence interval.

3.2.5 Other Classes of Antihypertensive Drugs

There is little evidence of the effects of other classes of antihypertensive treatment, including ACE inhibitors, α-blockers and angiotensin II receptor antagonists, on stroke prevention. Their use will be dictated by other considerations such as the presence of CHF in the case of ACE inhibitors, and also the necessity to use combined therapy in many patients to lower BPs to target levels, e.g. the combination of thiazide plus ACE inhibitor or angiotensin II antagonists.

3.2.6 Recommendations for Primary Stroke Prevention

Overall, an antihypertensive regimen based on low dose thiazide diuretics or particularly in those with isolated systolic hypertension, long-acting dihydropyridine calcium antagonists in addition to thiazides, would seem appropriate to prevent stroke in the group most at risk, the elderly. In patients with diabetes mellitus who are hypertensive, an ACE inhibitor or low dose thiazide diuretic appear at present to be the first-line drugs of choice.[36]

3.2.7 Target BP

In the Hypertension Optimal Treatment (HOT) study,[39] stroke risk was lowest when SBP was reduced to 142mm Hg and DBP to below 80mm Hg, and cardiovascular mortality was lowest at a BP of 139/87mm Hg. Therefore, it would seem reasonable to aim for a treated SBP of <150mm Hg

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Table VIII. Risk reduction given by odds ratios (OR) with 95% confidence intervals (CIs) for stroke, coronary heart disease (CHD) and total mortality in overviews of all randomised placebo-controlled antihypertensive trials using low dose thiazide diuretics and β-blockers and for those conducted in the elderly (>60 years) (adapted from Psaty et al.[30] and Messerli et al.[31])

	Patient group	Stroke OR (95% CI)	CHD OR (95% CI)	Total mortality OR (95% CI)
Low dose thiazide diuretics	All	0.64 (0.53-0.77)	0.71 (0.59-0.85)	0.87 (0.77-0.99)
Thiazide diuretics	Elderly	0.61 (0.51-0.72)	0.74 (0.64-0.84)	0.86 (0.77-0.96)
β-Blockers	All	0.71 (0.59-0.86)	0.93 (0.71-1.09)	0.94 (0.83-1.08)
β-Blockers	Elderly	0.75 (0.57-0.98)	1.01 (0.80-1.29)	1.05 (0.88-1.25)

and DBP of <90mm Hg in all patients with hypertension. In patients with diabetes mellitus and others at particularly high cardiovascular risk, tighter BP control may be desirable.

4. Secondary Prevention of Stroke

Patients at the highest risk of stroke include those with a history of cardiovascular disease, particularly previous stroke where recurrence rates vary from 7 to 14% in the first year to between 4 and 7% annually thereafter.[40] Clearly, patients at highest risk have the greatest potential to benefit from interventions that lower the risk. Because of intra/extracranial vascular disease, changes in cerebral autoregulation and hence cerebral blood flow (CBF) in patients who have had a stroke, the relationship between BP and stroke recurrence and the effect of lowering BP may differ from that seen in more healthy people.

4.1 Relationship of BP to Stroke Recurrence

Most, but not all, studies in patients with a history of stroke suggest that higher BP is associated with stroke recurrence.[41-43] Irie et al.[44] have reported a U-shaped relationship of stroke recurrence with DBP with the optimal DBP being 80 to 85mm Hg. However, in the UK Transient Ischaemic Attack (TIA) Study that included almost 2500 patients with TIA or minor stroke, there was a direct continuous relationship between both SBP and DBP and risk of further stroke, such that a reduction in SBP of 12mm Hg or DBP of 5mm Hg was associated with a 34% reduction in stroke risk.[45]

4.2 Effect of Antihypertensive Therapy on Stroke Recurrence

Five studies have considered the effect of antihypertensive therapy on stroke recurrence in patients with a remote history of stroke.[46-50] Three of these studies[47-49] individually did not show a significant reduction in stroke risk although a meta-analysis of all 5 studies showed a significant 28% reduction in further strokes (RR 0.72, 95% CI 0.61 to 0.85).[51] The largest study, the Poststroke Antihypertensive Treatment Study (PATS), was conducted in 5615 Chinese patients with minor stroke who were hypertensive or normotensive and received indapamide, a thiazide diuretic.[50] A mean BP fall of 5/2mm Hg was associated with a 29% reduction in stroke recurrence. Many of the patients enrolled in the above studies had a minor stroke or made a good recovery and tended to have a mean age lower than that expected. The effect of antihypertensive therapy in older patients with more extensive cerebrovascular disease is less clear. For example, concern has been raised about lowering BP and its effect on CBF and cerebral ischaemia in patients with severe carotid artery stenosis.

Based mainly on the results of the PATS study, it appears likely that antihypertensive therapy started weeks to months following stroke onset can reduce stroke incidence in patients who are making a good recovery but have persistently high BP. As in the primary prevention of stroke, thiazide diuretics may be suitable as the initial first choice for many patients during the chronic phase of secondary stroke prevention. A greater degree of certainty about the benefits of such therapy in patients with a history of stroke, and determination of the levels

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of BP at which to intervene will have to await the results of further trials such as the Perindopril Protection Against Recurrent Stroke Study (PROGRESS).[52] This study is examining the effect of an ACE inhibitor and thiazide diuretic primarily on stroke recurrence and secondarily on other cardiovascular events.

4.3 When to Start Antihypertensive Therapy Following Stroke

The discussion in section 4.2 considered antihypertensive treatment in the 'chronic' phase of stroke. Whether to intervene with antihypertensive therapy in the early poststroke phase, and at what stage, is unclear. There is evidence of a U-shaped relationship between BP immediately following stroke and short term outcome,[53] such that high SBP (>160mm Hg)[54] and low SBP (<140mm Hg) are associated with higher mortality.

4.4 Potential Risks and Benefits of Lowering BP in the Early Poststroke Period

There have been many case reports of neurological deterioration following administration of antihypertensive therapy in patients who have had a stroke, usually as a result of large BP falls.[55,56] Even moderate reduction in systemic BP may lead to falls in CBF if cerebral autoregulation is impaired as has been suggested following stroke.[57] Under such circumstances reduced cerebral perfusion may lead to further ischaemic damage, particularly to the potentially salvageable penumbral region surrounding the infarct. In contrast, maintenance of high BP may promote further oedema and haemorrhage.

4.5 Studies of BP Lowering in the Early Stroke Period

High BP immediately following stroke is common but tends to fall spontaneously over the ensuing 7 to 14 days.[58,59] Use of drugs with an antihypertensive action, such as β-blockers,[60] dihydropyridine calcium antagonists[61] and ion channel blockers,[62] in the early stroke period (within 48 hours) has been associated with poorer outcomes compared with placebo-treated groups. In the recent National Institutes of Neurological Disorders and Stroke thrombolysis trial with alteplase (rtPA), use of antihypertensive therapy by either active or placebo groups was not associated with a better outcome.[63]

4.6 Effects of Therapy on CBF Following Stroke

Use of ACE inhibitors in the first week following ischaemic stroke, either as a single dose or on a regular basis has been shown to lower systemic BP but not to reduce CBF.[64,65] However, this may not apply to other drugs such as dihydropyridine calcium antagonists[66] or cerebrovascular vasodilators such as hydralazine, sodium nitroprusside or nitrates.[67,68] β-Blockers and labetalol may have less effect on reducing CBF.[67,68]

4.7 Continuing or Stopping Antihypertensive Therapy Following Stroke

There are very little data on the effects of continuing antihypertensive therapy in those already treated prior to their stroke compared with giving no treatment or starting therapy. In a preliminary report, 24-hour BP changes over the first week were found to differ little whether therapy was continued or stopped following stroke onset compared with those patients receiving no therapy.[69] Only introducing therapy (a thiazide diuretic) led to a greater fall in systemic BP. Furthermore, in the early stroke period orthostatic BP falls were found to be infrequent in patients taking antihypertensive therapy and similar to those not receiving such treatment.[70]

The above considerations suggest that continuing certain classes of low dose antihypertensive therapy poststroke in the absence of a low BP may be better tolerated than initiating therapy in previously untreated patients. In clinical practice many doctors still continue antihypertensive therapy following stroke, and the potentially dangerous practice of routinely introducing treatment immediately following stroke in those with mild to

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moderate elevation of BP also occurs.[71] The Cochrane Collaboration is currently reviewing the data concerning the management of BP in the acute stroke period. To decide on best practice a controlled outcome study is required.

4.8 Recommendations for Managing High BP in the Early Poststroke Period

In the absence of relevant trial data only opinion-based recommendations on circumstantial evidence can be given. As BP tends to decline spontaneously in the first 7 to 10 days following stroke it would appear reasonable not to start antihypertensive therapy during this time in most patients. Therapy could be gradually introduced after the immediate poststroke period on the basis of BP measurements and the patient's condition if BP remains high.

Whether to continue previous antihypertensive therapy is unclear but can be guided by the clinical situation including factors such as level of BP, requirement for control of angina pectoris or CHF, and ease of drug administration in the presence of, for example, dysphagia or reduced consciousness level.

Indications for administering antihypertensive therapy in the immediate poststroke period are suggested in table IX. In the absence of firm or compelling indications (table IX, point A) there is little evidence to support the use of such therapy during this time, although some opinion suggests that sustained high BP in patients with uncomplicated cerebral haemorrhage should be treated cautiously to prevent re-bleeding and vasogenic oedema.[72]

Table IX. Suggested recommendations for managing high blood pressure (BP) in the early poststroke period

A. Firm indications for use of antihypertensive therapy
Malignant or accelerated hypertension i.e. DBP >130mm Hg
Hypertensive encephalopathy
High BP in the presence of compromised target organ function, e.g. myocardial ischaemia, aortic dissection, cardiac or renal failure
B. Less firm indications
Persistently high BP e.g. >200-220mm Hg over a period of many hours or days, particularly in the presence of cerebral haemorrhage or if associated with clinical deterioration
C. Little or no indication
Hypertension in patients with cerebral infarction, not associated with above conditions, i.e. the majority of patients following strokes

DBP = diastolic blood pressure.

5. Conclusion

There is now good trial evidence for the use of antihypertensive therapy in the primary prevention of stroke not only in patients with moderate to severe hypertension, but also in those with mild hypertension. Despite this, the older population who are most at risk of stroke, have the highest prevalence of hypertension and therefore the most to gain, are often inadequately treated or not even identified as having hypertension.[71] It is possible to identify a group of patients at high risk of stroke who would benefit from 'aggressive' BP lowering to target BP levels not often attained at present. For the secondary prevention of stroke, there is less conclusive evidence of the patient groups that benefit most from treatment, and at what BP levels and when treatment should be started. The available evidence suggests that many stroke patients with hypertension, particularly those who have had a minor stroke, will benefit from antihypertensive therapy introduced some weeks after stroke onset.

References

1. MacMahon S. Blood pressure and the prevention of stroke. J Hypertens 1996; 14 Suppl. 6: s39-46
2. Neilsen WB, Lindenstrom E, Vestvo J, et al. Is diastolic hypertension an independent risk factor for stroke in the presence of normal systolic blood pressure in the middle aged and elderly? Am J Hypertens 1997; 10: 634-9
3. Sacco RL, Chair MS, Benjamin EJ, et al. Risk factors. Stroke 1997; 28: 1507-17
4. Philips SJ, Withsnant JP. Hypertension and the brain. Arch Intern Med 1992; 152: 938-45
5. Thrift AG, MacNeal JJ, Forbes A, et al. Risk factors for cerebral haemorrhage in the era of well controlled hypertension. Stroke 1996; 27: 2020-5
6. Bland AD, Waite MA. von Willebrand factor and soluble e-selectin in hypertension: influence of treatment and value in predicting the progression of atherosclerosis. Coron Artery Dis 1996; 7: 143-7
7. Lip GYH, Blan AD, Zarifis J, et al. Soluble adhesion molecule p-selectin and endothelial dysfunction in essential hypertension: implications for atherogenesis? A preliminary report. J Hypertens 1995; 13: 1674-8
8. Fotherby M, Williams J, Forster L, et al. von Willebrand factor and monocyte adhesion are associated with pulse pressure and

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e-selectin with mean arterial pressure [abstract]. Age Ageing 1999; 28 (Suppl.): 20
9. Lottermoser K, Weisser B, Hertfelder HJ, et al. Antihypertensive drug treatment and fibrinolytic function. Am J Hypertension 1998; 11: 378-84
10. Bikkina M, Levi D, Evans JC, et al. Left ventricular mass and risk of stroke in an elderly cohort: the Framingham Heart Study. JAMA 1994; 272: 33-6
11. Gottdiener JS, Reda DJ, Massie BM, et al. The effect of single drug therapy on reduction of left ventricular mass in mild to moderate hypertension: comparison of six antihypertensive agents. Circulation 1997; 95: 2007-14
12. Jennings G, Wong J. Regression of left ventricular hypertrophy in hypertension: changing patterns with successive meta-analyses. J Hypertension 1998; 16 Suppl. 6: S29-34
13. Gottdiener JS, Reda DJ, Williams WW, et al. Effect of single drug therapy on reduction of left atrial size in mild to moderate hypertension: comparison of six antihypertensive agents. Circulation 1998; 98: 140-8
14. MacMahon S, Peto R, Kupler J, et al. Blood pressure stroke and coronary heart disease. Part I: prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335: 765-74
15. Dahlof B, Lindholm LH, Hansson L, et al. Morbidity and mortality in the Swedish Trial in Older Patients with hypertension (STOP – Hypertension). Lancet 1991; 338: 1281-5
16. Coope J, Warrender TS. Randomised trial of the treatment of hypertension in elderly patients in primary care. BMJ 1986; 293: 1145-51
17. Amery A, Birkenhager W, Brixco P, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly Trial. Lancet 1985; I: 1349-54
18. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. BMJ 1992; 304: 405-12
19. Management Committee. Treatment of mild hypertension in the elderly: a study initiated and administered by the National Heart Foundation of Australia. Med J Aust 1981; 2: 398-402
20. SHEP Co-operative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Programme (SHEP). JAMA 1991; 265: 3255-64
21. Staessen JA, Fagard R, Thijs L, et al. Randomised double blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997; 350: 757-64
22. Liu L, Wang G, Gong L, et al., for the Systolic Hypertension in China Collaborative Group. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. J Hypertens 1998; 16: 1823-9
23. Gueyffier F, Bulpitt C, Boissel J-P, et al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. INDANA Group. Lancet 1999; 353: 793-6
24. Curb JD, Pressel SL, Kupler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. JAMA 1996; 276: 1886-92
25. Tight blood pressure control and risk of macrovascular and microvascular complications in type II diabetes: UKPDS 38. UK Prospective Diabetes Study Group [published eratum appears in BMJ 1999; 318: 29]. BMJ 1998; 317: 703-13
26. Wolf PA, D'Agostino RB, Belanger AJ, et al. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991; 22: 312-8
27. Core Services Committee. Guidelines for the management of mildly raised blood pressure in New Zealand. Wellington, New Zealand: Ministry of Health, 1995
28. Fotherby MD, Potter JF. Potassium supplementation reduces clinic and ambulatory blood pressure in elderly hypertensive patients. J Hypertens 1992; 10: 1403-8
29. Fotherby MD, Potter JF. Effects of moderate sodium restriction on clinic and 24-hour ambulatory blood pressure in elderly hypertensive subjects. J Hypertens 1993; 11: 657-63
30. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first line agents: a systematic review and meta-analysis. JAMA 1997; 277: 739-45
31. Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first line therapy for hypertension in the elderly? A systematic review. JAMA 1998; 279: 1903-7
32. Gong L, Zhang W, Zhu Y, et al. Shanghai Trial of Nifedipine in the Elderly (STONE). J Hypertension 1996; 14: 1237-45
33. Joint National Committee on the Prevention and Detection, Evaluation and Treatment of High Blood Pressure. The 6th report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 1997; 157: 2430-46
34. Frischman WH, Furburg CD, Freedwald WT. Beta-adrenergic blockade for survivors of acute myocardial infarction. N Engl J Med 1984; 310: 830-7
35. Borhani NO, Mercuri M, Berani PA, et al. Final outcome results of the Multicentre Ispradipine Diuretic Atherosclerosis Study (MIDAS). A randomised control trial. JAMA 1996; 276: 785-91
36. Yusuf S. Calcium antagonists in coronary artery disease and hypertension. Time for re-evaluation? Circulation 1995; 92: 1079-82
37. Estacio RO, Jeffers B, Hiatt W, et al. The effect of Nizoldipine as compared with Enalapril on cardiovascular outcomes in patients with non-insulin dependent diabetes and hypertension. N Engl J Med 1998; 338: 645-52
38. Pahor M, Psaty BM, Ferberg CD. Treatment of hypertensive patients with diabetes. Lancet 1998; 352: 689-90
39. Hanson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood pressure lowering and low dose aspirin in patients with hypertension: principle results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998; 351: 1755-62
40. Jorgensen HS, Nakayama H, Reith J, et al. Stroke recurrence: predictors, severity and prognosis. The Copenhagen Stroke Study. Neurology 1997; 48: 891-5
41. Merit JV, Adams GF. Comparison of mortality rates in elderly hypertensive and normotensive hemiplegic patients. BMJ 1966; 2: 802-5
42. Meissner I, Whistnant JP, Garraway WM. Hypertension management and stroke recurrence in the community (Rochester, Minnesota, 1950-1979). Stroke 1988; 19: 459-63
43. Johnston JH, Beevers DG, Titterington BM. The importance of good blood pressure control in the prevention of stroke recurrence in hypertensive patients. Postgrad Med J 1981; 57: 690-3
44. Irie K, Yamagucuchi T, Minematsu K, et al. The J-curve phenomenon stroke recurrence. Stroke 1993; 24: 1844-9

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45. Rodgers A, MacMahon S, Gamble G, et al. Blood pressure and risk of stroke in patients with cerebrovascular disease. BMJ 1996; 313: 147
46. Carter AB. Hypotensive therapy and stroke survivors. Lancet 1970; I: 485-9
47. Hypertension Stroke Co-operative Study Group. Effect of antihypertensive treatment and stroke recurrence. JAMA 1974; 229: 409-18
48. Dutch TIA Trial Study Group. Trial of secondary prevention with atenolol after transient ischaemic attack on non-disabling ischaemic stroke. Stroke 1993; 24: 543-8
49. Ericsson S, Olofsson BO, Wester PO, for the TEST Study group. Atenolol in secondary prevention after stroke. Cerebrovasc Dis 1995; 5: 21-5
50. PATS Collaborating Group. Post stroke antihypertensive treatment study: a preliminary result. Chin Med J 1995; 108: 710-7
51. Gueyffier F, Boissel JP, Boutitie F, et al. Effect of antihypertensive treatment in patients having already suffered from stroke: gathering the evidence. The INDANA (INdividual Data ANalysis of Antihypertensive intervention trials) Project Collaborators. Stroke 1997; 28: 2557-62
52. PROGRESS Management Committee. Blood pressure lowering for the secondary prevention of stroke: rationale and design for PROGRESS. J Hypertens 1996; 14 Suppl. 2: s41-6
53. Philips SJ, Sandercock P, Slatter J. U-shaped relationship between systolic pressure and early death after acute ischaemic stroke [abstract]. Can J Neurol Sci 1995; 22 (1): s44
54. Robinson TG, Waddington A, Ward-Close SJ, et al. The predictive role of 24-hour compared to casual blood pressure levels on outcome following acute stroke. Cerebrovasc Dis 1997; 7: 264-72
55. Strandgaard S. Cerebral ischaemia caused by overzealous blood pressure lowering. Dan Med Bull 1987; 34 Suppl. 1: 5-7
56. Evidente V, Yagnik P. Blood pressure management in acute stroke [abstract]. Am Acad Neurol 1996; 46 (2 Suppl. 1): A256
57. Strangaard S, Paulson OB. Cerebral autoregulation. Stroke 1984; 15: 413-6
58. Britton M, Carlsson A, deFaire U. Blood pressure course in patients with acute stroke and matched controls. Stroke 1986; 17: 861-4
59. Harper G, Fotherby MD, Panayiotou BN, et al. The changes in blood pressure after acute stroke: abolishing the white coat effect with 24-hour ambulatory monitoring. J Intern Med 1994; 325: 343-6
60. Barer DH, Cruickshank JM, Ebrahim SB, et al. Low dose β-blockade in acute stroke (BEST) trial: an evaluation. BMJ 1988; 296: 737-41
61. Wahlgren NG, MacMahon OG, De Keyser J, et al., for the INWEST Study Group. Intravenous Nimodipine West European Stroke Trial (INWEST) of nimodipine in the treatment of acute ischaemic stroke. Cerebrovasc Dis 1994; 4: 204-10
62. Squire IB, Lees KR, Pryse-Philips W, et al. Lifarizine Study Group: a pilot safety study. Cerebrovasc Dis 1996; 6: 156-60
63. Brott T, Lu M, Kothari R, et al. Hypertension and its treatment in the NINDS rt-PA Stroke Trial. Stroke 1998; 29: 1504-9
64. Waldemar G, Vorstrup S, Anderson AR, et al. Angiotensin converting enzyme inhibition and lesional cerebral blood flow in acute stroke. J Cardiovasc Pharmacol 1989; 14: 722-9
65. Dyker AG, Grosset DG, Lees K. Perindopril reduces blood pressure but not cerebral blood flow in patients with recent cerebral ischaemic stroke. Stroke 1997; 28: 580-3
66. Lisk DR, Grotta JC, Lamki L. Should hypertension be treated after acute stroke? A randomised controlled trial using single photon emission computed tomography. Arch Neurol 1993; 50: 855-62
67. Teitlbaum JS. Management of blood pressure in acute neurological illnesses. Neurologist 1996; 2: 196-206
68. Tietjen CS, Hurn PD, Ulatowski JA, et al. Treatment modalities for hypertensive patients with intracranial pathology: options and risks. Crit Care Med 1996; 24: 311-22
69. Evans SN, Ahmed U, Fotherby MD. Effect of antihypertensive therapy on blood pressure after stroke [abstract]. Cerebrovasc Dis 1998; 8 Suppl. 4: 32
70. Panayiotou B, Reid J, Fotherby MD, et al. Orthostatic haemodynamic responses in acute stroke. Postgrad Med J 1999; 75: 213-8
71. Fotherby MD, Harper G, Potter JF. General practitioners management of hypertension in the elderly. BMJ 1992; 305: 705-2
72. Lavin P. Management of hypertension in patients with acute stroke. Arch Int Med 1986; 146: 66-8

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