HYPERTENSION AND STROKE

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Introduction
Stroke is the third most frequent cause of death after cancer and heart disease in developed countries and one of the most common reasons for developing cognitive impairment and vascular dementia [1]. High blood pressure (BP) is a major risk factor for stroke, and a continuous relationship between BP and the occurrence of stroke has been well established [2]. On the other hand, evidence from hypertension treatment trials has shown that relatively small reductions in BP (5–6 mm Hg in diastolic BP, 10–12 mm Hg in systolic BP over 3–5 years) reduce the risk of stroke by more than one third [3]. The primary prevention of stroke through antihypertensive therapy and BP control is well established. Likewise, higher BP levels after stroke increase the risk of recurrent stroke [4], and recent trials indicate that BP reduction with combined antihypertensive therapy is beneficial in reducing stroke recurrence [5].

Pathophysiology of vascular cerebral damage in essential hypertension
The brain is highly vulnerable to the deleterious effects of elevated BP. Systolic and diastolic hypertension in both men and women are well-established risk factors for the development of ischaemic and haemorrhagic stroke. Hypertension is a major risk factor for two distinct kinds of vascular problems: the complications of atherosclerosis, including cerebral infarction, and the complications of hypertensive small vessel disease, including intracerebral haemorrhage and lacunar infarctions, and cerebral white matter lesions (WML). In some cases, some of these lesions, such as lacunar infarcts and cerebral WML, may be silent and only detectable by radiological findings.

In the development and progression of chronic high BP, hypertensive cerebral angiopathy occurs, as do secondary reparative changes and adaptive processes, at all structural and functional levels of the cerebral vascular system (Table 1).

A family history of cerebrovascular disease and stroke is often perceived as a risk factor for stroke. The Framingham Heart Study found a positive association between a verified paternal or maternal history of stroke and an increased risk of stroke in offspring [6]. The inheritance is complex, multigenic, and heterogeneous. Associations with polymorphisms have been investigated in a variety of candidate genes, including haemostatic genes, genes controlling homocysteine metabolism and lipid metabolism, the angiotensin-converting enzyme (ACE) gene, and the endothelial nitric oxide synthase gene, with conflicting results which may reflect methodological difficulties, since many studies were small and underpowered or required careful case-control matching.

Relationship between high blood pressure and stroke risk
Hypertension represents a relative risk of stroke up to 6 times higher, while stroke is the most frequent complication in hypertensives [7]. In Western countries, ischaemic stroke accounts for approximately 80% of all stroke and haemorrhagic stroke for the remaining 20%. Incidence rates, commonly quoted at 2 per 1000 population, rise steeply from less than 1 per 1000 among people aged under 45, to more than 15 per 1000 among those aged 85 or more, but vary widely. In industrialized countries, approximately 75% of all strokes occur in people aged over 65 years. Around 80% of people survive the first four weeks following stroke and 70% survive for a year or more.

Overviews of large-scale observational studies have demonstrated that usual levels of BP are positively and continuously associated with the risk of stroke in a log-linear fashion [8]. This relationship between BP and stroke holds over a wide BP range, from systolic levels as low as 115 mm Hg and diastolic levels as low as 70 mm Hg [8]. Data from prospective observational studies indicate that usual levels of BP are directly and continuously related to the risk of initial stroke and a prolonged difference in usual BP levels of just 9/5 mm Hg is associated with an approximately one-third difference in stroke risk, with similar proportional effects in hypertensives and normotensives [2, 3]. Each 5–6 mm Hg reduction in usual diastolic BP is associated with a 38% lower risk of stroke [3]. Elevated BP is positively associated with both ischaemic and haemorrhagic stroke, but the association appears to be steeper for haemorrhagic stroke. The relationship between BP and stroke risk remains virtually unchanged after adjustment for serum cholesterol levels, smoking, alcohol, or a history of previous cardiovascular disease [10]. Similar associations appear to exist between BP and the risk of recurrent stroke although much of the evidence on recurrent stroke comes from smaller cohort and observational studies [8]. Data from the United Kingdom Transient Ischaemic Attack (UK TIA) Collaborative Group showed that a 10 mm Hg reduction in usual systolic BP was associated with a 28% reduction in the risk of recurrent stroke [4].

Although a continuous relationship between both systolic and diastolic BP and the occurrence of stroke has been well established, there is epidemiological evidence from the MRFF study that the systolic component of BP may exert a strong deleterious effect on cerebrovascular disease [9]. It is known that increased arterial stiffness results in increased characteristic impedance of the aorta and increased pulse wave velocity, which increase systolic and pulse pressures. Large-artery stiffness is the main determinant of pulse pressure. Data from the SHEP study show an 11% increase in stroke risk and a 16% increase in the risk of all-cause mortality for each 10-mm Hg increase in pulse pressure [10]. Laurent et al. [11], in a longitudinal study, found that aortic stiffness, assessed by carotid-femoral pulse wave velocity, is an independent predictor of fatal stroke in patients with essential hypertension.

Relationship between antihypertensive therapy and stroke prevention
Epidemiological studies have shown that each 5–6 mm Hg reduction in usual diastolic BP is associated with a 38% lower risk of stroke [3]. Clinical trials have also shown that a 10 mm Hg reduction in usual systolic BP was associated with a 28% reduction in the risk of recurrent stroke [4]. In addition, there is some evidence that antihypertensive drug treatment could play a role in the prevention of cognitive impairment or vascular dementia through BP control [12].

Primary prevention of stroke
It is generally believed that any of the commonly used antihypertensive drugs are effective in lowering the incidence of stroke, with larger reductions in BP resulting in larger risk reductions.

In the review by MacMahon [13] in 1996 of 17 randomized trials of antihypertensive treatment, a net BP reduction of 10–12 mm Hg systolic and 5–6 mm Hg diastolic conferred a reduction in stroke incidence of 38% (SD 4), with similar reductions in fatal and non-fatal stroke. Because the proportional effects of treatment were similar in higher and lower risk patient groups, the absolute effects of treatment on stroke varied in direct proportion to the background risk of stroke. The greatest potential benefits were observed among those with a history of cerebrovascular disease.

Table 1. Main pathophysiological cerebrovascular changes associated with high blood pressure

<table>
<thead>
<tr>
<th>Mechanical stress (endothelial lesion)</th>
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<tbody>
<tr>
<td>Endothelial dysfunction (loss of vasodilatory capacity)</td>
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<tr>
<td>Increased vascular permeability</td>
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<tr>
<td>Opened ionic channels</td>
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<tr>
<td>Hypertrophy of smooth muscle vascular vessels (reduced lumen)</td>
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<tr>
<td>Contraction of smooth muscle vascular vessels (increased vascular resistance)</td>
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<tr>
<td>Synthesis of collagen fibre (vascular stiffness)</td>
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<td>Transudation of plasmatic products to the arterial wall</td>
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In the overviews of randomised trials performed by the Blood Pressure Lowering Treatment Trials Collaboration (BPLTTC) [14] in 2000, the data showed that placebo-controlled trials of calcium antagonists reduced the risk of stroke by 39% [95% CI 15–56] and that placebo-controlled trials of ACE inhibitors reduced the risk of stroke by 30% [95% CI 15–43], with no significant differences between these two groups of regimens. More “intensive therapy” was associated with a 20% stroke risk reduction [95% CI 2–35] compared with “normal” BP reduction. The differences in BP between the two BP lowering strategies (“normal” versus “intensive”) were only 3 mm Hg. In the same line was the last review of the BPLTTC in 2008 (1990–2001) derived from 31 clinical trials [15]. In this review, reduction of BP produced benefits in younger (< 65 years) and older (≥ 65 years) adults, with no strong evidence that protection against major vascular events afforded by different drug classes varies substantially with age. In the recent HYVET [16] study, hypertensive patients over 80 years of age on active antihypertensive treatment showed a significant 39% reduction in fatal and non-fatal stroke (95% CI: [−51–13]; P = 0.06) compared with placebo. Furthermore, in a meta-regression analysis of 28 major trials in hypertensive or high risk patients, BP lowering was the major determinant in stroke prevention [17]. A mean BP fall of 10 mm Hg was associated with a decrease of approximately 25% in the incidence of stroke [17].

The statement on BP lowering and stroke prevention of the International Society of Hypertension [8] recommends any of the five classes of antihypertensive drugs: diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers (ARBs), because of the proportionate increase in risk. However, some trials in hypertensive patients have suggested a protective effect of ARBs in the primary prevention of stroke. The LIFE [18] study compared losartan and atenolol in hypertensive patients older than 55 years with electrocardiographically detected LHV. Losartan significantly reduced CV endpoints (13%), with minimal differences in BP changes between treatments. The beneficial effect of losartan was main-tained in patients with a mean reduction of 32/16 mm Hg compared with the placebo group (25% reduction; P = 0.001), with no differences on myocardial infarction or total mortality. The SCOPE [19] study included hypertensive patients aged 70–89 randomly assigned to candesartan or placebo with open-label active antihypertensive treatment added as needed. The primary composite endpoint, a combination of cardiovascular death, stroke, and myocardial infarction, was reduced by 10.9%, a difference that did not reach statistical significance. Of all the components of the primary endpoint, only the reduction in non-fatal stroke (27.8%; 95% CI: 1.3–47.2; P = 0.04) was statistically significant. However, there were marked differences in BP reduction (3.21/1.6 mm Hg) between candesartan and placebo treated patients.

Secondary prevention of stroke

The management of hypertension is important both during the acute phase of ischaemic stroke and throughout the long-term course of this condition. Both low BP and high BP, in the setting of acute stroke, are associated with poor outcomes. However, the optimal targets for patients with hypertension in the first few hours or days after stroke has not been established [20]. Some research has focused on antihypertensive therapy initiated in the first few days after stroke, but additional evaluation of the safety and efficacy of such therapy is needed, in the absence of definitive clinical data, current evidence-based guidelines suggest pursuing a cautious approach to reducing BP in the acute stroke setting. In many cases, the patient’s BP will decrease spontaneously during the first few hours after stroke, and no medical intervention will be needed.

A systematic review of the relationship between BP reduction and the secondary prevention of stroke and other vascular events [21] included 7 published, randomized controlled trials with a combined sample size of 15,527 participants with ischaemic or haemorrhagic stroke, studied from 3 weeks to 14 months after the event and followed up for 2 to 5 years. Treatment with antihypertensive drugs was associated with significant reductions in all recurrent strokes. The overall reductions in stroke and all vascular events were related to the degree of BP lowering achieved, while data on the relative benefits of specific antihypertensive regimens for secondary stroke prevention were not clear. Treatment was specifically designed to test the effects of a BP lowering regimen, including an ACE inhibitor, in 6105 patients with stroke or transient ischaemic attack within the previous 5 years. Randomization was stratified by intention to use single (perindopril) or combination (perindopril plus the diuretic indapamide) therapy in both hypertensive and normotensive patients. The combination of low BP (20 mm Hg) and a non-fatal stroke (95% CI: 30–54) reduction in the risk of recurrent stroke. The effects were present in both the hypertensive and normotensive groups. However, there was no significant benefit when the ACE inhibitor was given alone (reducing BP by an average of 5/3 mm Hg). Recently, the MOSES study of an ARB, eprosartan, on secondary stroke prevention found that the comparison of eprosartan versus nitrindipine in patients with a previous stroke resulted, despite a similar BP reduction, in fewer cerebrovascular and cardiovascular events in eprosartan treated patients [22]. A total of 1405 high-risk hypertensives in the last 24 months were randomized to eprosartan or nitrindipine (mean follow-up 2.5 years). The primary end point was the composite of total mortality and all cardiovascular and cerebrovascular events, including all recurrent events. The combined primary end point was significantly lower in the eprosartan group, mainly due to a reduction in cerebrovascular endpoints (37% reduction; P = 0.001). In the Elderly American Stroke Association and the European Stroke Organization [23] recommend antihypertensive treatment to prevent stroke recurrences. Because this benefit extends to persons with and without a history of hypertension, this recommendation should be considered for all ischaemic stroke and transient ischaemic attack patients (Class IIA; level of evidence B). Absolute target BP level and reduction are uncertain and should be individualized, but the benefit has been associated with an average reduction of 10/5 mm Hg, while normal BP levels have been defined as < 120/80 mm Hg (Class IIA; level of evidence B).

Summary and conclusions

Hypertension is the most important risk factor for stroke and may predispose to the development of more subtle cerebral damage based on arterial narrowing or pathological microvascular changes. Age and hypertension are responsible for silent structural and functional cerebral changes leading to cerebral WML, lacunar infarcts, and cognitive impairment. Prevention of stroke by antihypertensive therapy is well established, and trials indicate that BP lowering is also beneficial in reducing stroke recurrence even among stroke patients without a history of hypertension. Indeed, available data support the concept that BP reduction is individually effective, and that all available antihypertensive drugs are suitable to reach this goal. However, some evidence in both primary and secondary prevention suggests that the blockade of the renin-angiotensin system may be recommended.

References

14. Dahlöf B, Devereux RB, Kjeldsen SE, et al. ACE inhibitors and mortality in the cerebral circulation leading to cerebral WML, lacunar infarcts, and cognitive impairment. Prevention of stroke by antihypertensive therapy is well established, and trials indicate that BP lowering is also beneficial in reducing stroke recurrence even among stroke patients without a history of hypertension. Indeed, available data support the concept that BP reduction is individually effective, and that all available antihypertensive drugs are suitable to reach this goal. However, some evidence in both primary and secondary prevention suggests that the blockade of the renin-angiotensin system may be recommended.

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