

# Brain damage in hypertension

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## Abstract

Hypertension is the most important risk factor for stroke and may also predispose to the development of more subtle cerebral damage based on arteriolar narrowing or pathological microvascular changes. Age and high blood pressure are responsible for silent structural and functional cerebral changes leading to white matter lesions, lacunar infarction, and cognitive impairment. Some reports suggest that antihypertensive drug treatment and blood pressure control may play a role in preventing the progression of silent cerebrovascular damage, cognitive impairment and dementia. Prevention of stroke by antihypertensive therapy is well established, and recent trials indicate that blood pressure lowering is also beneficial in reducing stroke recurrence even among stroke patients with no history of hypertension. Early treatment of high blood pressure may prevent progression of silent structural and functional cerebral disease, with blood pressure reduction sustained to target values being the main priority for primary or secondary stroke prevention.

**Key words:** stroke, hypertension, silent cerebrovascular damage.

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Stroke is the third most frequent cause of death after cancer and heart disease in developed countries and is one of the most common causes of cognitive impairment and vascular dementia [1]. High blood pressure (BP) is a major risk factor for stroke, and a continuous relationship between BP and stroke is well established [2, 3]. 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 during 3-5 years) reduce the risk of stroke by more than one third [4]. Primary prevention of stroke through antihypertensive therapy and BP control is well established. Higher BP levels after stroke increase the risk of recurrent stroke [5], and recent trials indicate that reduction of BP with combined antihypertensive therapy is beneficial in reducing stroke recurrence [6].

Hypertension is known to be the most important factor for macrovascular cerebral complications such as stroke and, consequently, vascular dementia [2, 3, 7]. Hypertension may also predispose to the development of more subtle cerebral processes based on arteriolar narrowing or pathological microvascular changes. It has been suggested that cerebral microvascular disease contributes to the development of vascular cognitive impairment [8]. The mechanisms underlying hypertension-related cognitive changes are complex and not yet fully understood (Figure 1). Correlations between cerebral white matter lesions

(WML) and elevated BP provide indirect evidence that structural and functional changes in the brain over time may lead to reduced cognitive functioning when BP control is poor or lacking. In addition, there is some evidence that antihypertensive drug treatment could play a role in the prevention of cognitive impairment [9] or vascular dementia [10] through BP control.

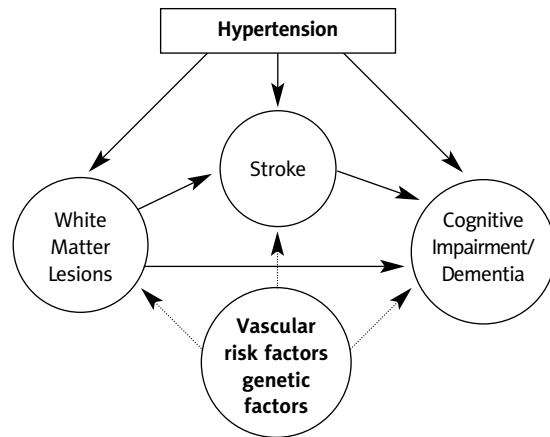
Cerebral WML are an important prognostic factor for stroke [11, 12], cognitive impairment [13] and dementia [14]. Older age and hypertension are constantly reported to be the main risk factors for cerebral WML [15]. Hypertensive patients have a higher rate and extension of cerebral WML compared with normotensives [15, 16]. In addition, it has been shown that treated, controlled hypertensive patients have a lower prevalence of WML than both untreated and treated but not controlled hypertensive patients [16]. Recent evidence strongly supports the idea that cerebral WML in hypertensive patients should be considered a silent early marker of brain damage.

### Pathophysiology of cerebrovascular 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 is a well established risk factor for ischaemic and haemorrhagic stroke. Hypertension is a major risk factor for two kinds of vascular problems: complications of atherosclerosis, including cerebral infarction, and complications of hypertensive small vessel disease, including intracerebral haemorrhage, lacunar infarctions and cerebral WML. Some of those lesions, such as lacunar infarcts and cerebral WML, may be silent and may only be detected by radiological findings.

Stroke can be classified on clinical grounds, clinico-radiological correlates or purely radiological findings. Briefly, with respect to infarct topography, infarcts can be divided into cortical (anterior cerebral artery, divisions of middle cerebral artery or posterior cerebral artery territory, together with external watershed infarcts) or subcortical (lacunar, striatocapsular, anterior choroidal artery territory, white matter medullary or internal watershed infarcts). Hypertension is more likely to be implicated in subcortical infarcts (lacunar infarcts, WML).

Chronic high BP is associated with hypertensive cerebral angiopathy, secondary reparative changes and adaptive processes at all structural and functional levels of the cerebral vascular system (Table I). Hypertension causes marked adaptive changes in the cerebral circulation, including increased brain vessel resistance and loss of the physiological mechanism of autoregulation. Hypertensive encephalopathy results from



**Figure 1.** Different connections among hypertension, white matter lesions, stroke and cognitive impairment

**Table I.** Main physiopathological cerebrovascular changes related to high blood pressure

Mechanical stress (endothelial lesion)
Endothelial dysfunction (lost of vasodilatory capacity)
Increased vascular permeability
Opened ionic channels
Hypertrophy of smooth muscle vascular vessels (reduced lumen)
Contraction of smooth muscle vascular vessels (increased vascular resistance)
Synthesis of collagen fibre (vascular stiffness)
Transudation of plasmatic products to arterial wall

a sudden, sustained rise in BP sufficient to exceed the upper limit of cerebral blood flow autoregulation. The cerebral circulation adapts to less severe chronic hypertension at the expense of changes that predispose to stroke due to arterial occlusion or rupture.

Stroke is a generic term for a clinical syndrome that includes focal infarction or haemorrhage in the brain, or subarachnoid haemorrhage. Atherothromboembolism and thrombotic occlusion of lipohyalinotic small-diameter end arteries are the principal causes of cerebral infarction. Microaneurysm rupture is the normal cause of hypertension-associated intracerebral haemorrhage. Rupture of aneurysms on the circle of Willis is the most common cause of non-traumatic subarachnoid haemorrhage.

Lacunar infarction is the infarct subtype most closely and directly associated with hypertension because of its high prevalence among clinical lacunar syndromes, and the hypertensive lipohyalinotic changes seen in small penetrating vessels at necropsy [17]. In other infarct types, the

**Table II.** Early cerebrovascular damage related to hypertension

<p><b>Functional abnormalities:</b></p> <ul style="list-style-type: none"> <li>• reduced cerebral blood flow</li> <li>• increased cerebrovascular resistance</li> <li>• reduced cerebral vasomotor reactivity</li> <li>• incipient cognitive impairment</li> </ul>
<p><b>Structural abnormalities:</b></p> <ul style="list-style-type: none"> <li>• vascular remodelling</li> <li>• lacunar infarct – small deep infarcts caused by penetrating arteriolar occlusive disease</li> <li>• white matter lesions – periventricular white matter lesions caused by subcortical hypertensive small vessel disease</li> </ul>

effect of hypertension is less direct and is mediated by its effects on atherogenesis in large extracranial or intracranial vessels. Lacunae are small infarcts or, occasionally, haemorrhages related to Charcot-Bouchard microaneurysms.

### Silent cerebrovascular damage

Tables I and II summarize the possible underlying pathological processes of early cerebrovascular damage and their association with functional changes.

#### Cerebral blood flow autoregulation and white matter lesions

High BP influences the cerebral circulation, causing adaptive vascular changes. Hypertension influences the autoregulation of cerebral blood flow by shifting both the upper and lower limits of autoregulatory capacity towards a higher blood pressure, while hypertensive patients may be especially vulnerable to hypotension [15, 17], which may play a role in silent cerebrovascular damage, such as WML. Increased cerebral vascular resistance could be due to narrowing of the small vessels by lipohyalinosis and micro-atherosclerosis. The effect of high BP on small vessels is well known, with vascular remodelling occurring in cerebral blood vessels during chronic hypertension. It has been suggested that this structural alteration impairs autoregulation, exposing the white matter to fluctuations in blood pressure. For this reason it has been hypothesized that changes in cerebral haemodynamics may play a role in the development of WML [17].

However, most studies have found no significant changes in resting cerebral blood flow in both normotensive and hypertensive individuals with silent WML, and there are contradictory findings on the relationship between vasomotor reactivity (or vasodilatory capacity) and WML. Kuwabara et al.

[18] reported a close relationship between cerebral haemodynamic reserve capacity, measured by positron emission tomography, and the severity of WML in hypertensive patients. Bakker et al. [19] confirmed the association between decreased vasomotor reactivity and WML, measured by transcranial Doppler in 73 elderly individuals, of whom 56% were hypertensives. Conversely, Chamorro et al. [20] showed preserved vasomotor reactivity in 41 patients (71% hypertensives) with silent WML and first-ever lacunar infarction, although they had increased cerebrovascular tone, measured by transcranial Doppler. We recently found an association between silent cerebral WML and increased cerebrovascular tone in middle-aged, never-treated essential hypertensive patients, without affecting either cerebral blood flow velocity or the vasodilatory capacity of cerebral vessels [21]. Using exogenous contrast-based perfusion MRI, O'Sullivan et al. [22] have recently shown that elderly hypertensive patients with WML have a significant reduction in the cerebral blood flow of normal-appearing white matter compared with hypertensives without WML, suggesting that hypoperfusion may be an early feature of WML. However, it remains unclear whether hypoperfusion is a primary pathogenic mechanism or simply a secondary effect of damaged tissue.

The main current hypothesis concerning the association between high BP and ischaemic WML is that long-standing hypertension causes lipohyalinosis of the media and thickening of the vessel walls, with narrowing of the lumen of the small perforating arteries and arterioles that nourish the deep white matter [15]. The perforating vessels, which originate in the cortical and leptomeningeal arteries, have a relatively poor anastomotic system, which makes the white matter vulnerable to cerebral ischaemia. Low BP has also been reported to be a risk factor for WML [15]. White matter lesions have also been reported to be associated with a history of stroke, lacunar infarcts, heart disease and atrial fibrillation, which are frequently associated with both hypertension and other vascular risk factors [15].

#### Brain microbleeds and high blood pressure

The research and clinical investigation of neurological disorders, especially stroke, has led to the frequent detection of small, apparently spontaneous, homogeneous round foci of low signal intensity on magnetic resonance imaging. These abnormalities are known as brain microbleeds (BMB) and were first described in the mid-1990s. Pathological hallmarks of old haemorrhages, some studies have shown that the deep perforating arteries feeding the areas of the brain harbouring BMB showed lipohyalinosis, amyloid deposits and

ruptured arteriosclerotic microvessels. A recent review found that BMB were significantly associated with hypertension and diabetes in healthy adults and hypertension in adults with cerebrovascular diseases [23]. The association with hypertension was robust in sensitivity analyses. Some studies have shown an association between BMB and lacunae and white matter lesions [23]. However, it is not clear whether BMB are useful diagnostic markers and a significant risk factor (for example, for stroke).

### Role of genetic factors in the pathogenesis of cerebrovascular damage

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 [24]. Concordance rates in twin studies have shown nearly a five-fold increase in stroke prevalence among monozygotic twins compared with dizygotic twins [25]. However, identification of individual causative mutations remains unanswered. Inheritance is complex, multigenic, and heterogeneous. Associations with polymorphisms in a variety of candidate genes have been investigated, including haemostatic genes, genes controlling homocysteine metabolism, lipid metabolism, the angiotensin-converting enzyme (ACE) gene, and the endothelial nitric oxide synthase gene, with conflicting results [26], which may reflect methodological difficulties, since some studies were small and underpowered or required careful case-control matching.

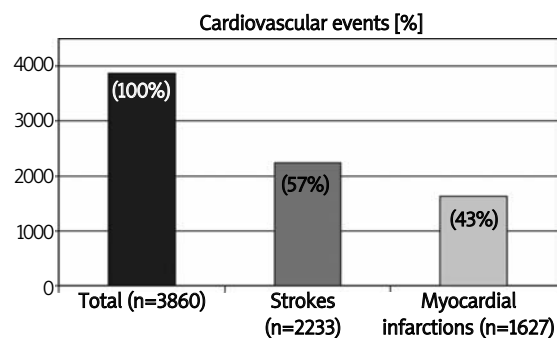
The ACE gene is probably the most widely investigated candidate gene in ischaemic stroke. Various studies have reported an association between an intron 16 insertion (I)/deletion (D) polymorphism of the ACE gene and stroke, with a relative risk of between 1.5 and 2.5, but other studies have found no significant association [26]. A meta-analysis that evaluated the risk of stroke in 1918 subjects vs. 722 controls from seven studies concluded that the ACE genotype conferred a small but modest effect, with an odds ratio of 1.31 [95% confidence interval (95% CI): 1.06-1.62], according to a dominant model of inheritance [27]. A variant of the angiotensinogen gene (M235T) has also been implicated in vascular disease, but its evaluation in stroke so far suggests that it is not an important risk factor. However, an epistatic interaction with the ACE gene has been proposed [28].

Genetic risk factors have been implicated in the presence and severity of cerebral WML but remain undetermined. A recent genetic study of elderly twins indicated that susceptibility to white matter hyperintensity on brain MRI was largely determined by genetic factors [29]. As previously mentioned,

genes contributing to inter-individual variation in BP levels and essential hypertension may play a role in the aetiology of WML or stroke, either through their effects on BP levels or through separate pathways. The renin-angiotensin system is an example of a system that may be involved in the pathogenesis of both hypertension and arteriosclerosis. Kario et al. [30] found a positive association between the angiotensin-converting enzyme D allele and both silent and clinically overt stroke in Japanese hypertensives. Sierra et al. [31] reported an association between the DD genotype or the D allele of the angiotensin-converting enzyme gene and WML in asymptomatic middle-aged hypertensive patients.

### Epidemiology of cerebrovascular damage

Hypertension represents a 6-fold increase in the relative risk of stroke [32]. Stroke is the most frequent complication in hypertensive patients (Figure 2) [33]. As mentioned, stroke is one of the leading causes of death worldwide and of disability in developed countries, and also a major disease in economic terms. Stroke has a considerable public health impact. In developed 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 in people aged <45 years to >15 per 1000 in people aged ≥85 years, but can vary widely [34]. In industrialized countries, approximately 75% of strokes occur in people aged >65 years. Around 80% of people survive the first four weeks following stroke and 70% survive for a year or more.



**Figure 2.** Number of fatal and non-fatal cerebral strokes, and myocardial infarctions reported in large prospective hypertension trials published after 1990. Adapted from Kjeldsen et al. [33]

#### 11 trials

(published during 1991-2000):

STOP-1, SHEP, STONE, SYST-EUR, SYST-CHINA, HOT, CAPPP, STOP-2, NICS, NORDIL, INSIGHT

**Randomized patients: 59 550**

Total strokes: 2233

Total myocardial infarctions: 1627

**Table III.** Prevalence of cerebral WML in different populations

Study	Population	Age [years]	Prevalence [%]
Breteler et al. [38]	111 subjects (40% hypertensives)	65-84	27
Liao et al. [16]	1920 subjects (49% hypertensives)	55-72	24.6
Longstreth et al. [37]	3301 subjects (44% hypertensives)	≥65	33.3
Shimada et al. [39]	20 hypertensives 28 normotensives	59-83	40 25
Goldstein et al. [40]	144 subjects	55-79	54.9
Lee et al. [42]	994 subjects (43% hypertensives)	20-78	5*
Sierra et al. [41]	66 hypertensives	50-60	40.9

\*Prevalence of both lacunae infarct and WML, age adjusted

Prevalence rates exceed 8 per 1000 adults, with a similarly marked age gradient [34], suggesting future pressure on health services. Disabilities are common and often severe among stroke survivors, requiring a substantial amount of informal care.

Cognitive impairment and dementia are one of the principal neurological disorders in the elderly. Aging is associated with a marked increase in the prevalence and incidence of degenerative and vascular dementia (VD). Alzheimer's disease and VD are the most common subtypes of dementia. The estimated prevalence is around 8% in people aged ≥65 years, and 15-20% in those aged >80 years [35]. Alzheimer's disease accounts for 50-60% of cases of dementia and VD for 30%. Hypertension is a major risk for cerebrovascular disease and therefore for VD. Traditionally, Alzheimer's disease has been thought to be a primary neurodegenerative disorder and not of vascular origin. However, emerging evidence supports the view that vascular risk factors and disorders may be involved in Alzheimer's disease [36-42].

#### Prevalence of cerebral white matter lesions

Various studies have examined the prevalence of WML in normotensive and hypertensive subjects with differing results (Table III). Differences in prevalence between studies may be due to subtle variations in WML assessment, but especially to the impact of risk factors, such as age and hypertension, which are influenced by study selection criteria. Most studies included both normotensive and hypertensive patients (untreated and treated), or subjects with a wide range of ages or only elderly people.

#### Prevalence of brain microbleeds

In the above-mentioned review, the prevalence of BMB was 5% in healthy adults, 34% in people with ischaemic stroke and 60% in people with non-traumatic intracerebral haemorrhage [23]. Brain microbleeds were more prevalent in patients with recurrent strokes than in those with first-ever strokes.

#### Relationship between high blood pressure and cerebrovascular damage

##### High blood pressure and risk of stroke

Overviews of large-scale observational studies have demonstrated that normal levels of BP are positively and continuously associated with the risk of stroke in a log-linear fashion [43]. This relationship between BP and stroke holds over a wide blood pressure range, from systolic levels as low as 115 mm Hg and diastolic levels as low as 70 mm Hg [43]. Data from prospective observational studies indicate that normal levels of BP are directly and continuously related to the risk of initial stroke, and a prolonged difference in normal 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 [3, 4]. Each 5-6 mm Hg reduction in usual diastolic BP is associated with a 38% lower risk of stroke [4]. Elevated BP is positively related to 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, and a history of cardiovascular disease [43]. Similar associations appear to exist between BP and the risk of recurrent stroke although much of the evidence comes from smaller cohort and observational studies [43]. Data from the United Kingdom Transient Ischaemic Attack (UK TIA) Collaborative Group show that a 10 mm Hg reduction in usual systolic BP was associated with a 28% reduction in the risk of recurrent stroke [44].

Although a continuous relationship between both systolic and diastolic BP and the occurrence of stroke is well established, there is epidemiological evidence from the MRFIT study that the systolic BP component may exert a strong deleterious effect on cerebrovascular disease (Figure 3) [45]. It is known that increased arterial stiffness results in increased

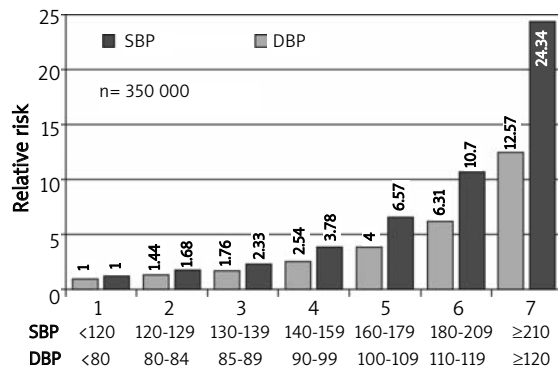
characteristic impedance of the aorta and increased pulse wave velocity, which increases systolic and pulse pressures. Large-artery stiffness is the main determinant of pulse pressure. Data from the SHEP study have shown an 11% increase in stroke risk and a 16% increase in all-cause mortality risk for each 10-mm Hg increase in pulse pressure [46]. Laurent et al. found [47], in a longitudinal study, that aortic stiffness, assessed by carotid-femoral pulse wave velocity, is an independent predictor of fatal stroke in patients with essential hypertension.

### High blood pressure and risk of cognitive impairment/dementia

As mentioned above, hypertension is known to be the most important factor for macrovascular cerebral complications such as stroke [7] and, consequently, vascular dementia [7]. Hypertension may also predispose to more subtle cerebral processes based on arteriolar narrowing or microvascular pathological changes. It has been suggested that cerebral microvascular disease contributes to vascular cognitive impairment [8]. Results from cross-sectional [48] and longitudinal [49-52] studies have shown a correlation between BP and cognitive function in the elderly. These studies have reported an association between high systolic BP (SBP) (the Honolulu-Asia Aging Study [50]), high diastolic BP (DBP) (the Uppsala Study [51]), elevated SBP and DBP (the Framingham Study [49]), or hypertension (National Heart, Lung, and Blood Institute Twin Study [52]) at midlife and impaired cognitive performance in late life. In addition, there is some evidence that antihypertensive drug treatment could play a role in the prevention of cognitive impairment [9] or vascular dementia [10] through BP control.

The mechanisms underlying hypertension-related cognitive changes are complex and not yet fully understood. It is unclear whether the impact of elevated BP on cognitive decline in late life is mediated through its chronic negative effect on the structural characteristics of the brain. Recent data have emphasized that high pulse pressure is associated with an increased risk of Alzheimer's disease [35]. Because increased pulse pressure is a clinical indicator of arterial stiffness, it may be postulated that functional changes in the arterial system are involved in the pathogenesis of dementia.

However, some studies have reported an increased incidence of dementia and Alzheimer's disease in people with low diastolic or systolic BP, especially in people aged  $\geq 80$  years [35]. The severity of atherosclerosis increases with age, resulting in high systolic BP and low diastolic BP in later life. Severe atherosclerosis in the very elderly as well as episodic or sustained hypotension, and possibly excessive treatment of hypertension, may



**Figure 3.** Relationship between cerebrovascular mortality and blood pressure values. Adapted from MRFIT. Stamler et al. [45]

induce cerebral hypoperfusion, ischaemia, and hypoxia in this age group.

Cerebral WML are an important prognostic factor for stroke [11, 12] or stroke recurrence [53-55], and also for cognitive impairment [13, 37, 38] and dementia [14]. Various studies have shown an association between cerebral WML and cognitive function in both normotensive and hypertensive elderly populations [13, 37, 56-58]. In a longitudinal study, De Groot et al. [13] examined the relationship between WML severity and cognitive decline over a 10-year period in 563 subjects aged 60-90 years and found that subjects with severe periventricular WML had more rapid cognitive decline. An association between WML in brain MRI and poorer neuropsychological test results were found in middle-aged, asymptomatic, never-treated essential hypertensives [57]. Hypertensive patients with WML had a significantly poorer digit span forward performance, a standardised measure of attention, and slightly lower scores on visual memory tests than hypertensives without WML [57]. In addition, a longitudinal study of 1077 people aged 60 to 90 years who underwent a brain MRI at baseline and were followed up for a mean of 5.2 years found that WML, especially in the periventricular region, increase the risk of dementia (76% for Alzheimer's disease, 13% for vascular dementia, 11% for other types of dementia) [14]. Likewise, the Cardiovascular Health Study found that people with more severe WML had a twofold increase in the risk of dementia [43]. In this study, 3608 participants with a brain MRI at baseline in 1991 were followed to 1998-1999. There were 480 cases of incident dementia, of which 330 (69%) were classified as Alzheimer's disease. The apolipoprotein E  $\epsilon 4$  genotype was also a powerful predictor of dementia.

Correlations between cerebral WML and elevated BP provide indirect evidence that structural and functional changes in the brain over time may lead to reduced cognitive functioning when BP control is poor or lacking. Skoog et al. [59] found an

association between elevated BP at age 70 and the development of dementia 10-15 years later, while patients with WML at age 85 had a higher BP at age 70, suggesting that previously increased BP may increase the risk of dementia by inducing small-vessel disease and WML. Likewise, Swan et al. [60] found that midlife SBP is a significant predictor of WML and decline in cognitive function.

In summary, WML, stroke, cognitive impairment and dementia are connected with hypertension and also with each other (Figure 1). However, the complex mechanisms that would explain all these relationships remain to be fully elucidated.

### High blood pressure and white matter lesions

The association between hypertension and WML has been established in cross-sectional [15, 16, 37-39] and longitudinal studies [61-63]. However, some reports have suggested that this relationship is only evident when 24-h ambulatory BP monitoring (ABPM) is used to assess BP. Goldstein et al. [40] found a correlation between WML and office systolic, but not diastolic, BP, in a group of elderly normotensive subjects. Conversely, the severity of WML correlated with both systolic and diastolic BP, measured by ABPM. In a group of mixed normotensives, "white coat" hypertensives and sustained hypertensives, Shimada et al. [39] also found a correlation between the number of lacunae and periventricular hyperintensities with 24-h BP, but not with office BP. Sierra et al. [41] found a correlation between WML and both clinic and 24-h ABPM in 66 untreated middle-aged hypertensive patients. This study also showed higher BP values (including office, 24-hour, daytime and nighttime estimates) among hypertensive patients with WML, compared with those without [41].

With respect to the circadian pattern of BP, Kario et al. [64] reported that both non-dippers and extreme dippers had significantly more silent cerebrovascular damage (measuring both lacunae and WML) than dippers. Although BP variability has been related to target organ damage in hypertension, its relationship with cerebral alterations has not been established. Goldstein et al. [40] suggested a higher standard deviation of waking SBP in patients with more severe WML. In contrast, neither the circadian rhythm nor the long-term variability of BP was related to WML in a group of 66 middle-aged never-treated hypertensive patients [41].

### Connecting left ventricular hypertrophy and white matter lesions as target organ damage

A number of studies have reported that echocardiographically-determined left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular morbidity and mortality in essential

hypertensive patients [65, 66]. Bikkina et al. [67] demonstrated that left ventricular mass (LVM) is associated with an increased risk of cerebrovascular events such as stroke and transient ischaemic attack in an elderly cohort from the Framingham Heart Study. It has also been proposed that left ventricular geometric patterns add prognostic information to both the development of cardiovascular disease [68] and extracardiac target organ damage in essential hypertension [69, 70]. Hypertensive patients with concentric LVH have more advanced target organ damage, including renal [69, 70] and retinal [70] involvement, than those with other patterns of left ventricular geometry. With respect to WML, several studies have shown an association between LVH and cerebral WML [37, 70-73], while others have not [39]. With respect to geometric patterns, a study found a close relationship between silent WML and concentric LVH in middle-aged untreated essential hypertensive patients, with WML being more common among patients with concentric LVH [73]. This association was independent of the degree of BP elevation. Another study has recently shown that LVH in middle-aged essential hypertensives is associated with a reduction in regional cerebral blood flow in the area of the cerebral striatum [74].

The mechanisms linking LVH with cerebrovascular damage are still unclear and may reflect long-term exposure to genetic, hormonal, or metabolic factors in addition to BP. It is difficult to differentiate the relative role of elevated BP from the direct contribution of LVH to the increased risk of developing cerebrovascular disorders, and longitudinal studies are necessary.

### Relationship between antihypertensive therapy and prevention of cerebrovascular damage

Epidemiological studies have shown that each 5-6 mm Hg reduction in usual diastolic BP is associated with a 38% lower risk of stroke [4]. Clinical trials have also shown that a 10 mm Hg reduction in usual systolic BP is associated with a 28% reduction in the risk of recurrent stroke [44]. In addition, there is some evidence that antihypertensive drug treatment could play a role in the prevention of cognitive impairment [9] or vascular dementia [10] through BP control.

### Primary prevention of stroke

In the review by MacMahon [75] in 1996 of 17 randomized trials of antihypertensive treatment, a net blood pressure reduction of 10-12 mm Hg systolic and 5-6 mm Hg diastolic conferred a reduction of 38% in stroke incidence (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 in patients with a history of cerebrovascular disease. The overviews of randomised trials by the Blood Pressure Lowering Treatment Trialists' Collaboration [76] in 2000 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 regimens. "More intensive therapy" was associated with a 20% reduction in the risk of stroke (95% CI 2-35) compared with "normal" BP reduction. The differences in BP between the two BP lowering strategies ("normal" vs. "intensive") were only 3 mm Hg. In a meta-analysis of 179,122 people from 28 clinical trials, antihypertensive treatment with calcium antagonists, but not with ACE inhibitors, significantly reduced stroke risk compared to diuretics/ $\beta$ -blockers [77]. The authors suggested that the anti-atherosclerotic effect of calcium antagonists observed in some studies could explain this association.

Later meta-analyses of randomized controlled trials confirmed an approximately 30 to 40% reduction in the risk of stroke with BP lowering [78]. The statement on BP lowering and stroke prevention of the International Society of Hypertension [43] recommends any of the five classes of antihypertensive drugs: diuretics,  $\beta$ -blockers, calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs), because the priority is BP reduction "per se". Likewise the latest review of the Blood Pressure Lowering Treatment Trialists' Collaboration [79] in 2008 included 190,606 people from 31 clinical trials. The results showed that blood pressure reduction with any of the five antihypertensive drug classes was associated with a lower risk of fatal and non-fatal stroke, both in people aged >65 years and those aged  $\leq$ 65 years.

However, some trials in hypertensive patients have suggested a protective effect of ARBs in the primary prevention of stroke. The LIFE [80] study compared losartan and atenolol in hypertensive patients aged >55 years with electrocardiographically detected LVH. Losartan significantly reduced CV endpoints (13%) with minimal differences in BP changes between treatments. The benefit of losartan was mainly due to a 25% reduction in the rate of stroke ( $P=0.001$ ), with no differences in myocardial infarction or total mortality. The SCOPE [81] 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 non-significant difference. 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 (3.2/1.6 mm Hg) between the candesartan and placebo groups.

#### A special situation: primary prevention of stroke in the very elderly

It is known that age and hypertension are the most important risk factors for stroke, which in fact is considered a disease of the elderly. Whether the treatment of patients with hypertension aged  $\geq$ 80 years is beneficial remained unclear until the recently published results of the HYVET study [82], which included 3845 patients aged  $\geq$ 80 years with sustained SBP of  $\geq$ 160 mm Hg. Patients were randomly assigned to receive the diuretic indapamide (sustained release 1.5 mg) or matching placebo. The primary endpoint was fatal or nonfatal stroke. In an intention-to-treat analysis, active treatment was associated with a 30% reduction in the primary endpoint ( $P=0.06$ ). The secondary endpoints showed a significant 39% reduction in deaths from stroke ( $P=0.05$ ), a 21% reduction in death of any cause ( $P<0.02$ ), and a 64% reduction in heart failure ( $P<0.001$ ).

#### Secondary prevention of stroke

A systematic review analysed the relationship between BP reduction and the secondary prevention of stroke and other vascular events [83]. The analysis included 7 published, randomized controlled trials with a combined sample size of 15,527 patients with ischaemic or hemorrhagic 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, but the relative benefits of specific antihypertensive regimens for secondary stroke prevention were not clear.

The PROGRESS [84] study 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 therapy reduced BP by a mean of 12/5 mm Hg and resulted in a 43% (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). In the recent MOSES study, 1405 high-risk hypertensives with cerebral events during the last 24 months were randomized to eprosartan (an ARB) or nitrendipine (mean follow-up 2.5 years). The primary endpoint was the composite of total mortality and all cardiovascular and cerebrovascular events, including all recurrent events. The study found that there were fewer cerebrovascular and cardiovascular events in eprosartan treated patients, despite a similar BP reduction [85]. The combined primary endpoint was significantly lower in the eprosartan group, mainly due to the reduction in cerebrovascular events.

In summary, in agreement with the American Heart Association recommendations [86], antihypertensive treatment is recommended for the prevention of recurrent stroke. 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 unclear and should be individualized, but the benefit has been associated with a mean reduction of  $\approx$ 10/5 mm Hg, and normal BP levels defined as <120/80 mm Hg (class IIa; level of evidence B).

#### Prevention of cognitive impairment/dementia

Both cross-sectional and longitudinal data from observational studies have shown some beneficial effects of antihypertensive treatment against cognitive impairment, cognitive decline and dementia in the elderly [35]. Three large-scale randomized placebo-controlled clinical trials have assessed the potential role of antihypertensive therapy in preventing cognitive impairment, dementia and stroke-related cognitive decline. The SHEP [87] study found that active treatment with thiazide diuretics significantly reduced the risk of stroke and cardiovascular events (primary endpoints), but not of cognitive impairment and dementia (secondary endpoints). However, re-analysis of the data indicated that differential drop-out rates between treatment and placebo groups might have obscured a potential effect of antihypertensive treatment against cognitive decline and dementia [88]. In the Syst-Eur trial, patients with isolated systolic hypertension were initially treated by nitrendipine, and if necessary with enalapril, or hydrochlorothiazide, or both. The results showed that active therapy reduced the incidence of dementia by 50% over 2 years [89]. After termination of the initial trial, all participants were continued on the active therapy for another 2 years in an open study whose results reinforced

the initial conclusion that long-term antihypertensive therapy initiated with a long-acting dihydropyridine calcium channel blocker reduced dementia risk by 55% (95% CI 24-73%) [10]. In the PROGRESS study on the prevention of recurrent stroke, the risk of dementia and cognitive decline were evaluated as a secondary endpoint. The results showed no significant effect of the therapeutic regimen on the overall risk of dementia. However, the regimen significantly reduced the risk of dementia with recurrent stroke by a third, the overall risk of cognitive decline by a fifth, and the risk of cognitive decline with recurrent stroke by a half [90]. The absence of a treatment effect on the overall risk of dementia might be due to the limited power of detecting a more modest effect and to premature discontinuation of active treatment by some patients. In addition, the SCOPE trial was initially designed to address whether candesartan-based antihypertensive therapy in older hypertensive patients reduced the risk of cardiovascular events, cognitive decline, and dementia. However, due to ethical concerns, the study was finally designed to compare candesartan and usual antihypertensive therapy regimens. After 4 years of observation, the trial found no significant difference in dementia incidence, cognitive decline and changes in mean mini mental state examination (MMSE) scores between the two groups [81]. The MOSES [85] study also had changes in cognitive function, measured by the MMSE, as a secondary endpoint, and the results showed no differences between groups.

In summary, despite the limitations and methodological differences, there is moderately strong evidence to support the view that hypertension in midlife, especially if not treated effectively, negatively affects cognition and contributes to the development of dementia, and even Alzheimer's disease, in late life. High BP in the middle-aged implies a long-term cumulative effect which leads to increased severity of atherosclerosis and more vascular comorbidities in late life. There is less evidence that the same negative effect on cognition is present for hypertension in later life. Indeed, some reports on the harmful cognitive effect of low BP suggest that in older adults, and particularly the very elderly, an appropriate level of BP may be required to retain cognitive function by maintaining adequate cerebral perfusion. However, optimum BP levels are unknown. Observational results suggest a protective effect of antihypertensive treatment against cognitive decline and dementia. Confirmation from randomized clinical trials is limited, and comes mainly from the Syst-Eur trial [89]. Other clinical trials showed either no clear treatment effect or only a beneficial effect against post-stroke dementia and cognitive decline.

### Antihypertensive therapy and early cerebral damage

Cross-sectional population-based MRI studies have shown that treated and controlled hypertensive patients have a lower prevalence of WML than both untreated and treated but not controlled hypertensive patients [16]. Van Dijk et al. [91] studied 1805 individuals aged 65 to 75 years from 10 European cohorts in whom blood pressure measurements were initiated 5 to 20 years before the brain MRI and found that patients with poorly controlled hypertension had a higher risk of severe WML than those without WML or those with controlled or untreated hypertension. Increased systolic and diastolic BP were associated with more severe WML and reduced diastolic BP was associated with more severe periventricular WML. The authors suggest that successful treatment of hypertension may reduce the risk of WML but that reducing diastolic BP may have a potentially negative effect on the occurrence of severe periventricular WML. However, the lack of difference between controlled and untreated hypertensives could be due to the fact that the untreated group had less severe hypertension or a shorter duration of hypertension. Another study performed on 845 subjects showed that hypertension at baseline was significantly associated with an increased risk of severe WML in the brain MRI at 4 years of follow-up. When both BP levels and antihypertensive drug intake were taken into account, the risk of severe WML was significantly reduced in subjects with normal BP taking antihypertensive medication compared with those with high blood pressure taking antihypertensive drugs [62].

In a longitudinal study, Schmidt et al. [92] evaluated volunteers aged 50-75 years without neuropsychiatric disease who underwent brain MRI at baseline and at 3 years (204 individuals) and 6 years (191 individuals) of follow-up. At 3 years, only diastolic BP and WML at baseline were significant predictors of white matter hyperintensity progression. At 6 years of follow-up, the grade of WML at baseline predicted progression of WML better than age and hypertension [92].

An MRI substudy of PROGRESS (Perindopril Protection Against Recurrent Stroke Study), a randomized trial of BP lowering with perindopril versus placebo in normotensive and hypertensive subjects with cerebrovascular disease, has recently found that the mean total volume of new WML was significantly reduced in the active treatment group compared with placebo [93]. A *post hoc* analysis also indicates that the greatest beneficial effect of antihypertensive therapy on WML progression was observed in patients with severe WML at entry.

### Neuroprotective effect of renin-angiotensin system blockade?

As mentioned, two large trials of primary prevention in hypertensive patients have shown that losartan [80] and candesartan [81] were superior to atenolol or conventional treatment in preventing stroke. In a smaller study of secondary prevention in hypertensive patients with a previous stroke, another ARB, eprosartan, was superior to nitrendipine in cerebrovascular protection [85]. Although it is always difficult to draw definite conclusions from different trials involving different types of patients and different drug comparisons, it seems that a picture of better cerebrovascular protection with ARB may be suggested by these trials. Several different (and probably complementary) mechanisms have been proposed to explain the better cerebrovascular outcomes in patients treated with ARB, including left ventricular hypertrophy regression, protection against atrial enlargement and supraventricular arrhythmias, effects on endothelial function, risk biomarkers and vascular remodelling, and specific neuroprotection mediated through the angiotensin II and the AT-2 receptor [94]. This better outcome is supported by some specific mechanisms related not only to the renin-angiotensin blockade but also to specific AT-1 receptor antagonism, increased angiotensin II and stimulation of the AT-2 receptor. The fact that some of these actions are not shared by ACE inhibitors helps to explain why this latter class of drugs has failed to provide significantly better protection against stroke than other conventional antihypertensive treatments, whereas trials based on ARB therapy have shown better cerebrovascular protection.

However, more and better evidence is necessary to establish their specific cerebrovascular properties.

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