



REVIEW ARTICLE

Cerebral complications of hypertension

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Ischaemic and degenerative brain diseases are a major health problem leading to a devastating loss of autonomy. Hypertension has been shown to carry an increased risk not only for cerebrovascular morbidity and mortality but also for cognitive impairment and dementia. Although diastolic blood pressure is considered an important risk factor, it is now clear that isolated systolic hypertension and elevated pulse pressure also play an important role in the development of brain complications. Therefore the treatment of these conditions must urgently become a widespread tool of prevention. All the randomised placebo-controlled trials completed for the last 30 years have shown a reduction in fatal and/or non-fatal strokes. In the most recent trials in isolated systolic hypertension in older patients, the benefit was even greater because of the higher risk in these populations. The new classes of drugs, in particular, calcium-channels blockers and angiotensin-

converting enzyme inhibitors, have been shown to be as effective as the originally used diuretics and beta-blockers. Active treatment in the Syst-Eur trial based on nitrendipine as first step, possibly associated with enalapril and/or hydrochlorothiazide reduced not only stroke and cardiovascular complications but also the incidence of dementia including Alzheimer's disease. This important finding must be confirmed by further trials specifically focusing on the prevention of dementia. In addition, the importance of pulse pressure as a risk factor, underlines the need for new drugs which could increase aortic distensibility and decrease systolic blood pressure without greatly reducing diastolic pressure. Improving the management of hypertension offers new opportunities to reduce age-related disease in older people and to promote healthy aging.

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Introduction

Ischaemic and degenerative brain diseases are a major health problem, particularly in the elderly, leading to a devastating loss of autonomy. Hypertension has been shown to carry an increased risk, not only for cerebrovascular morbidity and mortality but also for cognitive impairment and dementia. The fact that antihypertensive treatment has been demonstrated to decrease that risk offers a new opportunity to reduce the prevalence of such related disorders and to promote healthy aging. Although diastolic blood pressure is traditionally considered to be an important risk factor, it is now clear that isolated systolic hypertension and elevated pulse pressure also play an important role in the development of brain complications. Therefore the treatment of these conditions must urgently become a widespread tool of prevention.

Hypertension and stroke

Definition and methodological issues

Stroke is a generic term for a clinical syndrome that includes focal infarction or haemorrhage of the brain, or subarachnoid haemorrhage. Atherothromboembolism and thrombotic occlusion of lipohyalinotic small-diameter end-arteries are the principal causes of cerebral infarction. Micro-aneurysm rupture is the usual cause of hypertension-associated intracerebral haemorrhage. Rupture of aneurysms of the circle of Willis is the most common cause of non-traumatic subarachnoid haemorrhage. Research on stroke has been confused by the lack of standardised classification of stroke subtypes.¹

Stroke epidemiology

Stroke is a major cause of disability and mortality particularly among persons aged 65 years or older. Its incidence, as established by the USA National Survey, ranges from 5.8 to 18.2 per 1000 patient-years and rises exponentially with increasing age. The annual risk in individuals under 15 years is 1 in 100 000 while the risk in those aged 85 years and over is 1 in 33.²

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Mortality

Age-standardised mortality rates in people aged 40–69 years vary 10-fold from countries with high rates (24.0 and 14.4 per 10000 population in men and women respectively in Bulgaria) to those with low rates (2.9 and 1.8 in Switzerland).³ Stroke accounts for 10–12% of all deaths in industrialised countries; about 88% of the deaths attributed to this condition are observed in people over 65 years.

Data from many industrialised countries are consistent with a decline in stroke mortality of about 5% per year over recent decades.^{2,4–7} Earlier studies concluded that the decline in stroke mortality was mainly, but not only, due to the decreased incidence of cerebrovascular complications linked to primary prevention measures, especially the detection and treatment of hypertension. Although there was no reduction evidenced in some developed nations, as shown in Table 1,^{8–20} it may be speculated that hypertension treatment has contributed to the decline in stroke mortality, in particular by reducing the severity of acute stroke.¹⁸ Better emergency medical care may also have led to a decrease in case-fatality rate. In more recent years, the decline in stroke mortality continued, but at a slower rate of only 2 to 3% per year.²¹ This recent slow-down may be an artefact due to the increased detection of less severe cases of stroke by computed tomography.^{17,22}

Hypertension as a risk factor for strokes

Some non-modifiable risk factors include age, male gender, race and genetic factors. Modifiable risk factors (see in Table 2)²³ have been extensively reviewed and the predominant role of hypertension is underlined by all the epidemiological studies.^{23–25}

Hypertension increases the risk for transient ischaemic attacks²⁶ as well as the incidence of any type of stroke²⁴ including ischaemic stroke and focal

Table 1 Reported trend of stroke incidence in different parts of the world

Place (Author)	Changes	Period
Japan (Ueda, 1981) ⁸	Decrease	1961–1976
Japan (Shimamoto, 1989) ⁹	Decrease	1965–1983
Sweden (Harmsen, 1992) ¹⁰	No change	1971–1987
Framingham Study (Wolf, 1992) ¹¹	No change	1953–1983
New Zealand (Bonita <i>et al</i> , 1993) ¹²	No change	1981–1991
Hawai (Kagan, 1994) ¹³	Decrease	1969–1988
China (Cheng <i>et al</i> , 1995) ¹⁴	Decrease	1986–1990
East Germany (Eisenblätter, 1995) ¹⁵	Increase	1972–1980
Finland (Tuomilehto, 1996) ¹⁶	Decrease	1983–1992
Minnesota (Brown <i>et al</i> , 1996) ¹⁷	Increase	1950–1989
Portland (Barker <i>et al</i> , 1997) ¹⁸	No change	1967–1985
Minnesota (Shahar, 1997) ¹⁹	No change	1980–1985
Denmark (Truelsen <i>et al</i> , 1997) ²⁰	No change for persons aged 45 to 64 Decrease for men aged 65 to 84	1976–1993

Table 2 Modifiable risk factors for stroke (according to Sacco, 1995)²³

Stroke factors	Estimated relative risk	Estimated prevalence (%)
Hypertension	4.0–5.0	25–40
Cardiac disease	2.0–4.0	10–20
Atrial fibrillation	5.6–17.6	1
Diabetes mellitus	1.5–3.0	4–8
Cigarette smoking	1.5–2.9	4–8
Alcohol abuse	1.0–4.0	5–30
Hyperlipidaemia	1.0	6–50

intracerebral haemorrhage.²⁷ Data from the Framingham Heart Study show that hypertensive subjects have a three-fold greater risk of stroke than normotensive individuals and those with borderline hypertension have a 50% greater risk. In the 36 years follow-up of the Framingham Study, 56% of stroke incidence in men and 66% in women could be attributed directly to hypertension.¹¹ The risk of stroke rises proportionately with increasing blood pressure and systolic, diastolic, as well as combined hypertension have been proven to confer a substantial excess risk.²⁸ In the last 25 years, emphasis was laid on the deleterious influence of elevated diastolic blood pressure. Indeed, a meta-analysis of nine studies reported a 10 to 12-fold increase in the risk of stroke in the highest category of diastolic blood pressure (mean 105 mm Hg), as compared with the lowest (mean 76 mm Hg).²⁷ As a consequence, definition of hypertension and decisions for treatment were based essentially on diastolic blood pressure levels. However, as stressed by Black (1999),²⁹ since more than 25 years, systolic blood pressure has been proven to be a stronger predictor of cardiovascular diseases than diastolic blood pressure.³⁰ In the Multiple Risk Factor Intervention Trial (MRFIT) about 40% of strokes were attributable to elevation of systolic blood pressure above 140 mm Hg.³¹ A 10-year longitudinal survey demonstrated that the association between systolic blood pressure and the incidence of strokes persisted at highly advanced ages.³² On the whole, it has been consistently demonstrated for three decades that isolated systolic hypertension is the greatest risk factor for cerebrovascular complications other than age.^{33–35} Furthermore, a recent meta-analysis of eight trials has again shown that in untreated patients, systolic blood pressure was a more accurate predictor of mortality and cardiovascular complications, in particular, of strokes, than diastolic blood pressure. Since at any given level of systolic blood pressure, mortality increased in the face of decreasing diastolic pressures, pulse pressure is bound to be considered as a risk factor in its own right, and should be examined as such.³⁶

Recurrence of strokes

Hypertension as well as other risk factors including cardiac disease, diabetes mellitus, heavy alcohol consumption and smoking may increase the risk of recurrence which ranges from 3 to 8% in the first 30 days and from 25 to 40% in the 5 years following

the first occurrence of stroke.²³ To a similar extent, the incidence of stroke is also increased after a transient ischaemic attack in the presence of hypertension or other associated vascular risk factors.^{37,38} The risk of developing stroke ranges from 30 to 50% in the 5 years after a first attack with a peak occurring in the first year.

Treatment: evidence from trial data

Primary prevention of strokes

The identification of hypertension as a risk factor led to the possibility of prevention by controlling elevated blood pressure. All randomised controlled trials run for 30 years have shown the clinical benefit of treating hypertensive people with antihypertensive drugs, mainly diuretics and beta-blockers as first-line treatment (VA study,³⁹ HDFP,⁴⁰ Australian therapeutic trial,⁴¹ MRC trials,⁴² STOP,⁴³ EWPHE,⁴⁴ SHEP,⁴⁵ Syst-Eur,⁴⁶ Syst-China;⁴⁷ see Table 3). All of these have provided evidence for a reduction both in fatal and non-fatal strokes. Most trials were guided by the level of diastolic blood pressure.⁴⁸ In a meta-analysis, Mulrow (1994)⁴⁹ calculated that a 5–6 mm Hg decrease in diastolic blood pressure is likely to induce a 40–45% decrease of stroke risk in middle-aged and older people.

More recent outcome trials focused on isolated systolic hypertension in older patients aged 60 years and over in whom antihypertensive treatment induced a significant reduction in stroke.^{45–47} The SHEP trial was still based on a thiazide as the first-line antihypertensive drug whereas Syst-Eur and Syst-China used the calcium-blocker nitrendipine, as initial treatment, with angiotensin-converting enzyme (ACE) inhibitors and/or diuretics as subsequent or alternative choice. A meta-analysis by Staessen *et al* (2000)³⁶ showed that in 15693 patients with isolated systolic hypertension enrolled in eight trials, antihypertensive treatment reduced stroke by 30%. Total mortality also decreased by 13%, cardiovascular mortality by 18%, all cardiovascular complications by 26%, and coronary events by 23%. Treatment prevented strokes more effectively than coronary events. Since systolic blood pressure at entry was correlated with strokes and

total mortality while diastolic blood pressure was not, the authors proposed that the benefit of treatment was essentially attributable to the reduction in systolic blood pressure.

Treatment of hypertension in the elderly

Because of the higher risk of cardiovascular disease in the elderly, the effect of antihypertensive treatment appears greater in patients over 60 or 65 years when expressed as an absolute risk reduction.⁵⁰

Two meta-analyses illustrated the benefit of antihypertensive treatment in older patients: Thijs *et al* (1992)⁵¹ showed that treating hypertension in patients aged 60 years and over reduced stroke mortality by 33%, coronary mortality by 26%, and all-cause mortality by 9%. Insua *et al* (1994)⁵² showed a significant benefit in total and cardiovascular morbidity and in all cardiovascular events. The reduction in stroke mortality and morbidity was 36% and 35% respectively. An overview of controlled studies on the effects of antihypertensive treatment in the elderly is shown on Table 3.

The EWPHE trial, in patients with systolic and diastolic hypertension, failed to demonstrate a significant benefit above the age of 80.⁴² However, the Syst-Eur trial evidenced a significant reduction in morbidity but not in mortality in this age group.⁵³ Gueyffier *et al* (1999),⁵⁴ in a meta-analysis of data from 1670 participants over 80, suggested that treatment of very old hypertensive patients prevented stroke by 34% (95% CI 8–52). Rates of major cardiovascular events and heart failure were significantly decreased, by 22% and 39% respectively. Although there was no reduction in cardiovascular mortality (and a non-significant increase in non-cardiovascular deaths), because of the observed benefit on morbidity, there is no firm reason to abandon the usual treatment recommendations in patients over 80. More information is needed though, and will hopefully be provided by the HYVETT trial.⁵⁵

The safety as well as the benefit of treating elderly patients with stage 1 isolated systolic hypertension (systolic blood pressure 140–159 mm Hg and diastolic blood pressure <90 mm Hg) remains to be determined by ongoing and planned placebo-controlled trials.

Table 3 Overview of controlled trials on the effects of antihypertensive treatment in the elderly

<i>Trials</i>	<i>Age</i>	<i>Stroke risk reduction (% treated vs control)</i>	<i>All cardiovascular disease (% treated vs control)</i>
Hypertension Detection and Follow-up Program Cooperative Group (1979) ⁴⁰	60–69	44	16
Management Committee of the National Heart Foundation of Australia (1981) ⁴¹	60–69	33	31
EWPHE (Amery <i>et al</i> , 1985) ⁴²	≥60	36	29
STOP-Hypertension (Dalh�f <i>et al</i> , 1991) ⁴³	70–84	47	40
MRC Working Party (1992) ⁴⁴	65–74	25	17
SHEP Cooperative Research Group (1991) ⁴⁵	≥60	33	32
Syst-Eur (Staessen <i>et al</i> , 1997) ⁴⁶	≥60	38	26
Syst-China (Liu <i>et al</i> , 1998) ⁴⁷	≥60	38	37

Antihypertensive treatment in diabetes mellitus

The effect of antihypertensive treatment in diabetes mellitus which carries a high cardiovascular risk has also been investigated in several studies. The SHEP study (1996)⁵⁶ showed that the benefit of low-dose diuretic treatment was similar in both diabetic and non-diabetic older patients. In contrast, the Syst-Eur trial based on the dihydropyridine calcium-channel blocker nitrendipine as the first-line antihypertensive drug, showed a greater reduction in total and cardiovascular mortality and cardiovascular complications in diabetic than in non-diabetic patients.⁵⁷ In line with this, the UK Prospective Diabetes Study group (1998),⁵⁸ the HOT trial⁵⁹ and the CAPPP trial⁶⁰ also confirmed the enhanced benefit of antihypertensive treatment in diabetic patients. This emphasises the need to strictly attain the goal blood pressure through treatment in these high risk patients.

Influence of the class of drugs

The majority of the intervention trials in hypertension have been run with diuretics and beta-blockers as first-line drugs. The efficacy and the safety of these two classes of drugs have been demonstrated in the elderly.^{42–45,61,62} The benefit of the newer antihypertensive agents has been proven more recently. The Shanghai Trial of Nifedipine in the Elderly,⁶³ Syst-Eur,⁴⁶ Syst-China⁴⁷ and NICS-EH Study Group trials⁶⁴ have shown that calcium-channel blockers are particularly effective in the prevention of cardiovascular and cerebrovascular complications in older patients. The HOPE and the CAPP studies have also demonstrated the clinical benefit of ACE inhibitors in the prevention of stroke and other cardiovascular complication of hypertension. In the HOPE study,⁶⁵ the ACE inhibitor ramipril, was shown to reduce the rate of death, myocardial infarction, and stroke even in normotensive patients of middle and older age with a high risk of cardiovascular events. The STOP-2 study showed similar effectiveness of beta-blockers and diuretics, angiotensin-converting enzyme inhibitors and calcium antagonists in the prevention of cardiovascular mortality or major events.⁶⁶

Blacher *et al* (2000)⁶⁷ have highlighted the role of pulse pressure as a major cardiovascular risk and emphasised the need for randomised trials with antihypertensive drugs which act differently on the pulsatile component of blood pressure. Those authors have suggested that vasopeptidase inhibitors and nitric oxide donors may possibly increase the distensibility of large arteries and reduce pulse pressure. Smulyan and Safar (2000)⁶⁸ and Staessen (2000)³⁶ also underline the interest of new drugs which could increase aortic distensibility and decrease systolic blood pressure without substantially reducing diastolic blood pressure.

Currently, several other possible ways of preventing strokes are being addressed including the role of lipid-lowering treatment alone or associated with antihypertensive drugs⁶⁹ and the value of low doses of aspirin together with antihypertensive drugs. In the HOT study, the latter association has

been shown to reduce cardiac infarcts but not strokes.⁵⁹ The HOT study also tried to determine the appropriate goal blood pressure level of therapy in 19000 patients with hypertension who were given a felodipine-based regimen.

As shown in a WHO review,⁷⁰ 36 trials are now in progress and should help to give further information on the still unanswered questions.

Secondary prevention of strokes

While the benefit of antihypertensive treatment is largely proven in terms of primary prevention, the effect of antihypertensive agents in secondary prevention is less well documented. However a meta-analysis⁷¹ has shown that in hypertensive stroke survivors, adequate blood pressure lowering drug treatment decreases stroke recurrence by 28%. The latter effect is smaller than that observed in primary prevention. The Progress Study⁷² will provide further information on this issue. Likewise, carotid endarterectomy in patients with more than 70% stenosis of the carotid artery, the use of antiplatelets agents and proper control of hypertension and other risk factors were shown to reduce significantly strokes in patients with transient ischaemic attacks.²⁴

Management of hypertension in general populations

Management of hypertension in the community is disappointing. Around 15% only of the patients are adequately treated.⁷³ Less than 30% patients on hypertensive drugs attain the JNC-VI goal for blood pressure control (<140 and <90 mm Hg) both in the US and in Europe.^{59,74–76} Therefore, important improvement remains to be made.

Moreover the new indication of pulse pressure as the most powerful risk factor must lead doctors to consider systolic blood pressure rather than diastolic blood pressure when determining treatment goals. The development of drugs which lower systolic pressure more than diastolic pressure and which would increase vascular distensibility over and above their blood pressure lowering effect, must be stimulated.^{29,36,68}

Secondary prevention is also unsatisfactory. Joseph *et al* (1999)⁷⁷ have shown that half of the patients followed for 2 years in a stroke clinic remained hypertensive. None of the smokers had stopped smoking and glucose levels were still high in 11 out of 16 patients suffering from diabetes mellitus.

Hypertension and cognitive function

Prevention of cognitive impairment and dementia is one of the most important challenges for the 21st century. Indeed, the increase in life expectancy is associated with a sharp rise in cognitive disorders, particularly after the age of 80.⁷⁸ The identification and management of risk factors for these invalidating and distressing conditions must be considered a priority.

Hypertension has been suspected to alter cognitive function. However opinion remains divided, because of methodological issues including: (1) differences in the study populations (age, level of education, duration of hypertension, volunteers, referrals, or population samples) (2) differences in the neuropsychological tests used to evaluate the participants; and (3) the use of cross-sectional rather than longitudinal study designs.^{79,80}

Cross-sectional studies

Many cross-sectional studies have attempted to determine whether cognitive function is related to hypertension.^{79,81–91}

Cognitive function has been found to be negatively, positively or not associated with systolic blood pressure or diastolic blood pressure (Table 4). In the studies that demonstrated a significant positive correlation between cognitive impairment and hypertension, the neuropsychological domains predominantly affected were learning and memory, attention and mental flexibility.

Steward (1999)⁸⁰ has suggested that the direction of association might be dependent on age. Cognitive impairment was associated with hypertension in younger subjects whereas it was related to low blood pressure in subjects over 75.⁹²

Similar findings have been reported in dementia studies. Hypertension was associated with Alzheimer's disease in subjects 69–78 years⁹³ and low blood pressure was associated with both Alzheimer's disease and vascular dementia in subjects

aged 75–101 years.⁹⁴ As suggested by the Rotterdam study,⁹² co-morbid disorders such as peripheral arterial diseases might explain the relationship between cognitive impairment or dementia and low blood pressure.

Longitudinal studies

Longitudinal studies are more appropriate to study possible role of blood pressure in cognitive deterioration (Table 5). Most of these studies suggest that chronic hypertension may alter cognitive functions. High mid-life blood pressure has been shown to be a strong and independent predictor of later cognitive impairment.^{90,95–98,100} Wilkie and Eisdorfer (1971)⁹⁵ showed that patients aged 60 to 69 with diastolic blood pressure >105 mm Hg at baseline had lower cognitive function 10 years later. In the Framingham cohort, Elias *et al* (1995)⁹⁷ observed that cognitive performance was negatively correlated with diastolic and systolic blood pressure measured at 12 to 14-year intervals. The Honolulu-Asia Aging study demonstrated a significant correlation between mid-life systolic blood pressure and the risk of cognitive impairment 25 years later.⁹⁸ In the Uppsala cohort, cognitive functions at 70 years of age correlated negatively with blood pressure measured at age 50 years of age.⁹⁰

In a longitudinal study by Skoog *et al* (1996),¹⁰¹ the patients who developed either Alzheimer's disease or vascular dementia, between ages 79 and 85, had mean blood pressure levels higher than those without dementia at age 70. However, during follow-up, blood pressure levels decreased in demented and non-demented patients, but the decrease was larger in the former. The decrease in blood pressure may be due to some pathological processes also affecting cognitive functioning. In

Table 4 Cross-sectional studies

Author	Results
Wallace, 1985 ⁸¹	Negative correlation with diastolic hypertension but not isolated systolic hypertension
Farmer, 1987 ⁸²	No relation
Sherr, 1991 ⁸³	No relation Relation diastolic BP (+10 mm Hg, OR = -0.8; 95% CI = -1.8; 0.2)
Desmond, 1993 ⁸⁴	No relation
Kuusisto, 1993 ⁸⁵	Negative correlation with systolic and diastolic blood pressure
Starr, 1993 ⁸⁶	Negative correlation with systolic and diastolic blood pressure
Gale, 1996 ⁸⁷	Negative correlation with diastolic blood pressure
Cacciatore, 1997 ⁸⁸	Cognitive impairment is related to diastolic but not systolic blood pressure protective effect of antihypertensive drugs
Guo, 1997 ⁸⁹	Positive correlation with systolic and diastolic blood pressure
Kilander, 1997 ⁹⁰	Negative correlation with ambulatory systolic and diastolic blood pressure
Van Boxtel, 1997 ⁹¹	No relation
Seux, 1998 ⁷⁹	Negative correlation with systolic blood pressure

Table 5 Longitudinal studies

Author	Results
Wilkie, 1971 ⁹⁵	Correlation hypertension and intellectual loss over years but not for borderline hypertension at age 60–69
Elias, 1993, 1995 ^{96,97}	Positive correlation with diastolic and systolic blood pressure
Launer, 1995 ⁹⁸	Cognitive impairment is related to systolic blood pressure but not diastolic blood pressure
Guo, 1997 ⁸⁹	Cognitive impairment is related to low blood pressure (systolic blood pressure <130 mm Hg) in untreated subjects and to high blood pressure (systolic blood pressure ≥180 mm Hg) in patients treated with antihypertensive drugs
Kilander, 1997 ⁹⁰	Negative correlation with diastolic blood pressure high scores for patients with diastolic blood pressure <70 mm Hg
Okumiya, 1997 ⁹⁹	J-curve relation between blood pressure and decline in MMSE score
Tzourio, 1999 ¹⁰⁰	Correlation between hypertension and intellectual impairment

addition, the observed blood pressure decrease may be a consequence of dementia. Some studies that included very old patients reported a J-curve relationship with a higher cognitive impairment in the subjects with the lowest and highest blood pressure.^{89,94,99,102}

As underlined by Glynn (1999),¹⁰³ the relationship between cognition and blood pressure is complex and different factors should be taken into account including: (1) age and education; (2) other cardiovascular risk indicators such as diabetes mellitus, hypercholesterolaemia and hyperinsulinaemia which may potentiate the negative effects of high blood pressure on cognitive functions;⁸⁴ and (3) duration of follow-up. In treated patients, whether or not cognitive decline may be due to initial hypertension or to treatment-induced reduction in blood pressure or to possible deleterious effects of the antihypertensive drugs may be difficult to appreciate.

The mechanism by which chronic hypertension alters cognitive functions remains to be elucidated. Chronic hypertension leads to vascular remodelling with narrowing of the lumen and wall thickening.¹⁰⁴ This may affect cerebral blood flow and disturb cerebral metabolism and structure. The negative effect of high blood pressure levels on intellectual performance could also be linked to alterations in the cerebral white matter, as suggested by the Rotterdam study which has highlighted the predominant role of risk factors for atherosclerosis in the development of brain lesions and cognitive deterioration.^{105,106}

Hypertension and white matter lesions

Leucoaraiosis and white matter lesions refer to white matter hypodensities on computed tomography and hyperintensities on T2-weighted MRI images, respectively. The pathogenesis and clinical correlates of age-related white matter lesions are still unclear. Controversial results in the literature are not surprising in view of inter-observer variations in the measurement of white matter lesions and intellectual impairment. Moreover, white matter lesions are relatively non-specific radiographic lesions which may be produced by a variety of pathophysiological processes. In the elderly, white matter lesions are predominantly found in patients with vascular risk factors and cerebrovascular diseases, and in subjects with various degrees of mental deterioration.¹⁰⁷

The main risk factors for white matter lesions are hypertension, particularly high systolic blood pressure,^{101,108,109} although some authors have reported either no or an inverse association with blood pressure.^{94,110,111} White matter lesions have also been associated with vascular risk factors including history of stroke,^{105,110} heart disease,^{105,110} atrial fibrillation¹¹⁰ and diabetes mellitus.¹¹²

The main hypothesis regarding the cause of white matter lesions is that long-standing hypertension may cause lipohyalinosis and thickening of the vessel walls with narrowing of the lumen of the small perforating arteries which could lead to ischaemia in the terminal distribution territories of these vessels, ie, deep white matter. Episodes of hypotension

related to aging, antihypertensive medications or cardiac failure may lead to hypoperfusion and hypoxia-ischaemia and consequently to loss of myelin in the white matter.¹¹³

Hypertension and overt dementias

Vascular dementia

Risk factors for vascular dementia have been extensively reviewed^{114,115} and hypertension appears the strongest.^{104,116–118} A significant correlation with hypertension exists in all forms of vascular dementia.^{118–121} Other risk factors include increasing age,¹²² low education,¹²³ coronary heart disease,^{122,124} atrial fibrillation,¹²⁵ diabetes,^{126–128} transient ischaemic attacks and cerebrovascular accidents,¹²⁴ high hematocrit level¹²⁰ and smoking.¹²⁶

Alzheimer's disease

Alzheimer's disease is a primary degenerative dementia and the issue of a possible vascular component was not addressed until recently. Indeed, clinical criteria used in most research studies to establish the diagnosis of probable Alzheimer's disease specifically exclude cases with symptoms or signs of cerebrovascular diseases.^{129–131} Some studies have found an inverse relationship between the occurrence of Alzheimer's disease and hypertension.^{94,132,133} In the Hisayama study, hypertension was a risk factor for vascular dementia but not for Alzheimer's disease; the 7-year incidence of vascular dementia decreased in men, along with progress in antihypertensive treatment in Japan, while the prevalence of Alzheimer's disease remained unchanged in men and women suggesting that hypertension does not play a major role in the pathogenesis of Alzheimer's disease in Japanese.¹²⁰

In contrast, in Western populations, several studies have suggested that hypertension may play a role in the development of Alzheimer's disease.^{118,134} Alzheimer's disease has been reported to be associated with other vascular risk factors^{115,135} including coronary heart disease,¹³⁶ atrial fibrillation,¹²⁵ diabetes mellitus,¹²⁷ and white matter lesions.¹³⁷ In the Rotterdam study, Hofmann (1997)¹⁰⁶ has demonstrated that indicators of atherosclerosis are associated with both Alzheimer's disease and vascular dementia, particularly in patients with the apolipoprotein E4 genotype. The characteristic lesions of Alzheimer's disease are also present, though to a lesser degree in vascular dementia and normal elderly people. Moreover, amyloid angiopathy, a common feature of vascular dementia is also common in Alzheimer's disease. So, in term of the hallmark lesions, there is important overlap between the two diseases that may well reflect common risk factors. Kokmen *et al* (1996)¹³⁸ studied the incidence of post-stroke dementia and found that there was a nine-fold increase in the risk of vascular dementia in the year following stroke, but the same study also observed a 50% increase in the risk of developing Alzheimer's disease. It is probable that cerebrovas-

cular diseases decrease the threshold of dementia in the individuals with Alzheimer lesions. Alternatively, Alzheimer's disease and cerebrovascular disease may share similar risk factors or etiologic pathways including, in addition to hypertension, also genetic factors, oxydative stress, psychological stress, increased permeability of the blood brain barrier.¹¹⁵ Indeed, the borders between Alzheimer's disease and vascular dementia are less strictly determined, both conditions sharing the same mechanisms at different degrees. It is, now, certainly more appropriate to consider dementia, as a whole, particularly in prevention trials.

Post-stroke dementia

Stroke significantly increases the risk for dementia.^{138–141,143} Prevalence rates vary between 13.6%¹⁴⁰ and 31.8%¹⁴² at 3 months. Kokmen *et al* (1996)¹³⁸ have shown that the cumulative incidence of dementia in a stroke cohort increased from 7% at year 1 to 48% at year 25. Furthermore this relationship may actually be underestimated since asymptomatic stroke may be a significant factor in the development of dementia.¹²⁰ Several studies have also shown that subtle cognitive changes without dementia are also frequently observed early after stroke.^{139,142} However, unrecognised pre-stroke dementia may contribute to the apparent onset of dementia after an ischaemic stroke and lead to an overestimation of the incidence of so-called post-stroke dementia.¹⁴⁴ As shown in Table 6, 5.5 to 16.3% of patients admitted for stroke seem to have had undetected pre-existing progressive cognitive decline.^{138,142,144–147}

Risk factors for post-stroke dementia

At least three different groups of factors, each acting independently, rather than a single pathophysiological mechanism probably contribute to the development of post-stroke dementia:^{111,148} (1) stroke-related factors such as the location and the severity of the brain lesions;^{149,150} (2) the overall cardiovascular risk profile as determined by the presence of atrial fibrillation¹⁴⁰ or diabetes mellitus;¹⁴⁹ (3) non-stroke-related factors similar to those found in Alzheimer's disease including increasing age,^{149,151} low education,¹⁴⁹ cortical atrophy.^{145,152} Hypertension has been identified as a risk factor by Pohjasvaara *et al* (1998),¹¹¹ but not by Skoog *et al* (1996).¹⁰¹ In addition to those risk factors, coexisting Alzheimer's disease pathology may also play a role, as indicated

by the number of patients with pre-stroke cognitive decline and presumed coexisting degenerative disorder.¹³⁸

Prevention of dementia and antihypertensive treatment

Prevention of dementia being a major issue – with hypertension as a main identifiable risk factor – has led to the inclusion of this outcome in several recent trials run in the elderly hypertensive patients.^{44–46} The Vascular Dementia project, set up within the framework of the double-blind placebo-controlled Syst-Eur trial, was the first to demonstrate a reduction in the incidence of dementia.

The Syst-Eur substudy¹⁵³ was run in non-demented patients, at least 60 years old, with isolated systolic hypertension randomised to active ($n = 1238$) or placebo treatment ($n = 1180$). Treatment was initiated with nitrendipine (10–40 mg/day) eventually associated with enalapril (5–20 mg/day) and/or hydrochlorothiazide (12.5–25 mg/day). Cognitive function was assessed by the Mini Mental State Examination.¹⁵⁴ The diagnosis of dementia was based on the DSM-III-R criteria. The etiology of dementia was assessed by the Modified Ischemic Score with brain imaging or if a brain scan was not possible by the Hachinski score. Median follow-up was limited to 2.0 years because of early termination of the trial, because a significant benefit for stroke, the primary outcome had been demonstrated. By intention-to-treat, the incidence of dementia was reduced by 50% from 7.7 in the placebo group to 3.8 cases per 1000 patient-years in the active treatment group (21 vs 11 patients, $P = 0.05$). Interestingly, but not surprisingly, the incidence of Alzheimer's disease was reduced even stronger than that of vascular or mixed dementia.¹⁵³ By contrast, in the SHEP trial, active treatment based on diuretics and beta-blockers failed to decrease the incidence of dementia. The mechanism of dementia prevention remains speculative. The negative SHEP results argues against a pivotal protection by purely lowering blood pressure. An additional (or alternative) still speculative explanation, could involve specific neuroprotection conferred by calcium-channel blockade.^{155,156} The potential importance of the Syst-Eur results in terms of public health policies warrant confirmation by other trials. The SCOPE trial based on the angiotensin II receptor blocker candesartan is underway¹⁵⁷ and the OPERA study using the vasopeptidase inhibitor, omapatrilat, is just starting. In these ongoing trials, dementia will be a secondary outcome. The risk is not negligible that an early reduction in the primary endpoints may curtail the possibility to evaluate the effects of treatment on prevention of dementia *per se*. A new trial specifically focusing on the prevention of dementia is therefore urgently needed. The European Working Party on High Blood Pressure in the Elderly (EWPHE) is planning such a study under the acronym DEPHY (Dementia Prevention in Hypertension) comparing diuretic-based vs dihydropyridine calcium antagonist-based treatment in the prevention of dementia in elderly hypertensive patients.

Table 6 Prevalence of cognitive decline prior to stroke

Studies	Prevalence of pre-stroke cognitive decline (%)
Tatemichi <i>et al</i> , 1990 ¹⁴⁵	8
Tatemichi <i>et al</i> , 1992 ¹⁴⁶	9.6
Andersen <i>et al</i> , 1996 ¹⁴⁷	5.5
Kokmen <i>et al</i> , 1996 ¹³⁸	8.4
Hénon <i>et al</i> , 1997 ¹⁴⁴	16.3
Pohjasvaara <i>et al</i> , 1997 ¹⁴²	12.2

The question has been raised whether excessive blood pressure reduction might have adverse effects on cognitive functions in older people. In the MRC trial, diuretics or beta-blockers did not influence cognitive function.¹⁵⁸ The SHEP study based on chlortalidone was successful in preventing strokes without unwanted effect on quality of life including cognition, emotional state, physical function, or leisure activities.¹⁵⁹

Moreover the results of the non-randomised, observational, Kungsholmen Project showed that antihypertensive treatment and particularly, but not only, diuretics may protect against dementia in the elderly.¹⁶⁰ Furthermore, the HOPE study also showed that long-term blood pressure control by diuretics or ACE inhibitors may reverse cognitive impairment associated with pre-existing hypertension.¹⁶¹

A deleterious effect of calcium channel blockers on cognitive function has been suspected in a cross-sectional study¹⁶² and in a 5-year prospective study.¹⁶³ However, in these two observational studies, confounding by indication was a potential source of bias. The placebo-controlled Syst-Eur trial refuted this effect noticed in non randomised studies.

Conclusions

In conclusion, hypertension is closely associated with stroke, and probably also with loss of cognitive function and dementia. Isolated systolic hypertension, or increased pulse pressure, now seem to be the best predictors of cerebral complications. Antihypertensive treatment reverses the risk and reduces stroke incidence. The risk of dementia is as yet not tied in that tightly with isolated systolic hypertension as compared with stroke, but may well qualify for adequate pharmacological prevention eg, based on appropriate antihypertensive treatment. The question remains whether calcium channel blockade might indeed be confirmed in playing such a prominent role. The comparative DEPHY (Dementia Prevention in Hypertension) trial aims to compare conventional (diuretic) and more recent (calcium channel blocker) treatment on equitable terms with regard to conventional endpoints and to the prevention of cognitive outcome and dementia.

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