In: Research Progress in Alzheimer's Disease and Dementia ISBN 978-1-60021-960-3
Editor: Miao-Kun Sun, pp. 381-413

Chapter XV

DEMENTIA AND HYPERTENSION

Jan A. Staessen[1,*], *Tom Richart*[1], *Lutgarde Thijs*[1] *and Willem H. Birkenhäger*[2]

[1]Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Belgium;
[2]Erasmus University, Rotterdam, The Netherlands.

ABSTRACT

Traditional teaching subdivides the dementia syndrome into neurodegenerative Alzheimer's disease (AD), vascular dementia (VaD), and mixed variants. In spite of the vast and continuing literature on the dichotomy between AD and VaD, new emerging concepts highlight the role of cardiovascular risk factors in the pathogenesis of AD, especially in older patients. Hypertension is the major player in the pathogenesis of stroke, poststroke dementia, and VaD. AD is the most common cause of dementia, contributing from 45% to 75% of the cases in Asians and whites, respectively. This review will focus on the role of hypertension as a reversible risk factor in the development of dementia, in particular AD. To set the stage, we will first summarize current insights in the epidemiology of AD, the pathogenesis of VaD and AD, and the association between neurodegeneration and atherosclerosis.

Dementia is characterized by gradual loss of memory, inability to learn, loss of vocabulary, communication skills and abstract thinking, disorientation in time and space, indifference, depression, delusions, loss of autonomy, and ultimately depersonalization and alienation. Traditional teaching subdivides the dementia syndrome into neurodegenerative

* Correspondence concerning this article should be addressed to: Dr. Jan A. Staessen, MD, PhD, FESC, FAHA, Studies Coordinating Centre, Laboratory of Hypertension, Campus Gasthuisberg, Herestraat 49, Box 702, B-3000 Leuven, Belgium. Telephone: +32-16-34-7104 (office); +32-15-41-1747 (home); +32-47-632-4928 (mobile); Facsimile: +32-16-34-7106 (office); +32-16-34-5763 (office); +32-15-41-4542 (home); email: jan.staessen@med.kuleuven.be; voicemail: jan.staessen@proximus.be.

Alzheimer disease (AD), vascular dementia (VaD), and mixed variants. In spite of the vast literature on the "dichotomy" between AD and VaD, recent concepts highlight the role of cardiovascular risk factors in the pathogenesis of AD as well, especially in older patients [1-7]. However, the nature of the association between AD and vascular pathology awaits further elucidation. Some researchers consider AD as a secondary event related to atherosclerosis of the extracranial and intracranial arteries. An alternative hypothesis is, that AD and atherosclerosis are convergent processes, sharing common pathogenetic mechanisms in the brain and in the arterial wall, such as disturbances of cholesterol transport, inflammation, and misfolded proteins [6].

Together with smoking and dyslipidemia, hypertension explains most of the modifiable cardiovascular risk in the population at large. It is the major player in the pathogenesis of stroke, poststroke dementia, and VaD. AD is the most common cause of dementia, contributing from 45% to over 75% of the cases in Asians and North Americans, respectively [8]. This review, which has been published previously in a shorter format, [9] will focus on the role of hypertension as a potentially reversible risk factor in the development of dementia, in particular AD. To set the stage, we will first summarize current insights in the epidemiology of AD, the pathogenesis of VaD and AD, and the association between neurodegeneration and atherosclerosis.

EPIDEMIOLOGY OF DEMENTIA

Across 36 cross-sectional studies, the prevalence of dementia ranged from 0.3% to 1% in subjects aged 60 to 64 years [8]. It exponentially increased to 10% - 20% in octogenarians and to over 40% in the ninth decade of life [8]. In a systematic review of 15 longitudinal studies, the incidence of dementia showed a similar age-related dependency with rates expressed in cases per 1000 person-years ranging from 0.4 to 4 at 60–64 years and from approximately 20 to over 40 per 1000 person-years at 80–85 years [8]. The 2003 World Health Report [10] estimated that worldwide adults aged 60 years or over lost around 8.6 million Disability Adjusted Life Years (DALYs) because of AD or other dementias. In terms of millions of DALYs lost in this age group, only ischemic heart disease (31.5), cerebrovascular disease (29.6) and chronic obstructive pulmonary disease (14.4) caused more premature disability and mortality [10].

Falling birth and death rates predict an unprecedented demographic revolution. At the beginning of this century, about 600 million of the world's population was 60 years or older. This number will double by 2025 and by 2050 reach two billion, the overwhelming majority of whom will be living in developing countries. [10] Currently 24.3 million people have dementia with an annual incidence of 4.6 million new cases [11]. In view of the age dependency of cognitive impairment, the number of patients with dementia will increase twofold every 20 years to 81.1 million by 2040, with over 60% living in developing countries [11]. In the United States, the number of demented patients with roughly triple from 4.6 million in 1998 to 16 million by 2050 [12]. The interaction or convergence between disease processes leading to cardiovascular disorders and dementia hopefully holds promise toward

the search for effective and common prevention of both of these disabling and burdensome conditions worldwide.

PATHOGENESIS OF DEMENTIAS

Vascular Dementia

VaD is caused by ischemic or hemorrhagic cerebrovascular disease, or by ischemic brain injury resulting from cardiovascular or circulatory disorders [13,14]. Poststroke dementia is the most common form of VaD [15]. In North American patients aged 60 years or more, the prevalence of dementia 3 months after an ischemic insult was 26.3%, about 9 times higher than in matched controls [16]. In another series of hospitalized patients with a first lacunar infarct, the 4-year incidence of dementia was 23.1% [17].

VaD may result from a single stroke interrupting brain circuits critical for memory and cognition (strategic infarct dementia) or from multiple strokes (multi-infarct dementia) [13,14]. Subcortical VaD has a more insidious character without the sensory-motor manifestations associated with stroke, but with progressive changes in personality, mood, behavior or cognition [13,14].

Alzheimer Disease

AD is a neurodegenerative disease with an inexorably progressive, disabling and fatal course (Figure 1), of which the clinically overt phase usually spans from 3 to 10 years [2]. The disease primarily affects cholinergic neurotransmission in the medial temporal lobe, the entorhinal cortex, and the hippocampus [2,18,19]. Interaction between these brain structures plays a crucial role in memory consolidation, memory optimization during sleep, and spatial orientation [20]. The prevailing viewpoint on the pathogenesis of AD rests on the extra- and intra-neuronal accumulation of misfolded protein, amyloid β-peptide (Aβ), which starts a pathogenetic cascade resulting in neurotoxicity [2,21].

Neurofibrillary tangles are the main histopathologic hallmark of AD [2,21,22]

NEURODEGENERATION AND ATHEROSCLEROSIS

Numerous neuroimaging [24-27] and post mortem histopathologic [3,23,28-30] studies indicate that up to one third of AD patients have some degree of vascular pathology, whereas in a similar proportion of VaD patients AD lesions are also present. Especially in older patients, increasing evidence suggests a strong link between AD, cardiovascular risk factors, and atherosclerosis. According to the Neuropathology Group of the Medical Research Council Cognitive and Ageing Study, [3] these observations illustrate how much present research on AD is based on a simplified view of the disorder as the conventional amyloid plaque cascade is not reflected in the brain pathology of a large number of demented people,

particularly in the age groups at the highest risk. A more balanced view is that the summation of vascular brain lesions, white matter damage reflecting small vessel disease, and typical AD pathology interactively lead to dementia, even when each type of lesion, on its own, would not be severe enough to cause dementia [15]. To complete the picture, current evidence suggests that cholinergic neuronal processes are not only involved in cognition per se, but in the preservation of cerebral blood flow as well (Figure 2) [7,31-33]. Indeed, cholinergic agents stimulated regional cerebral blood flow both in human volunteers [33] and in patients with AD [31-33] or VaD [31].

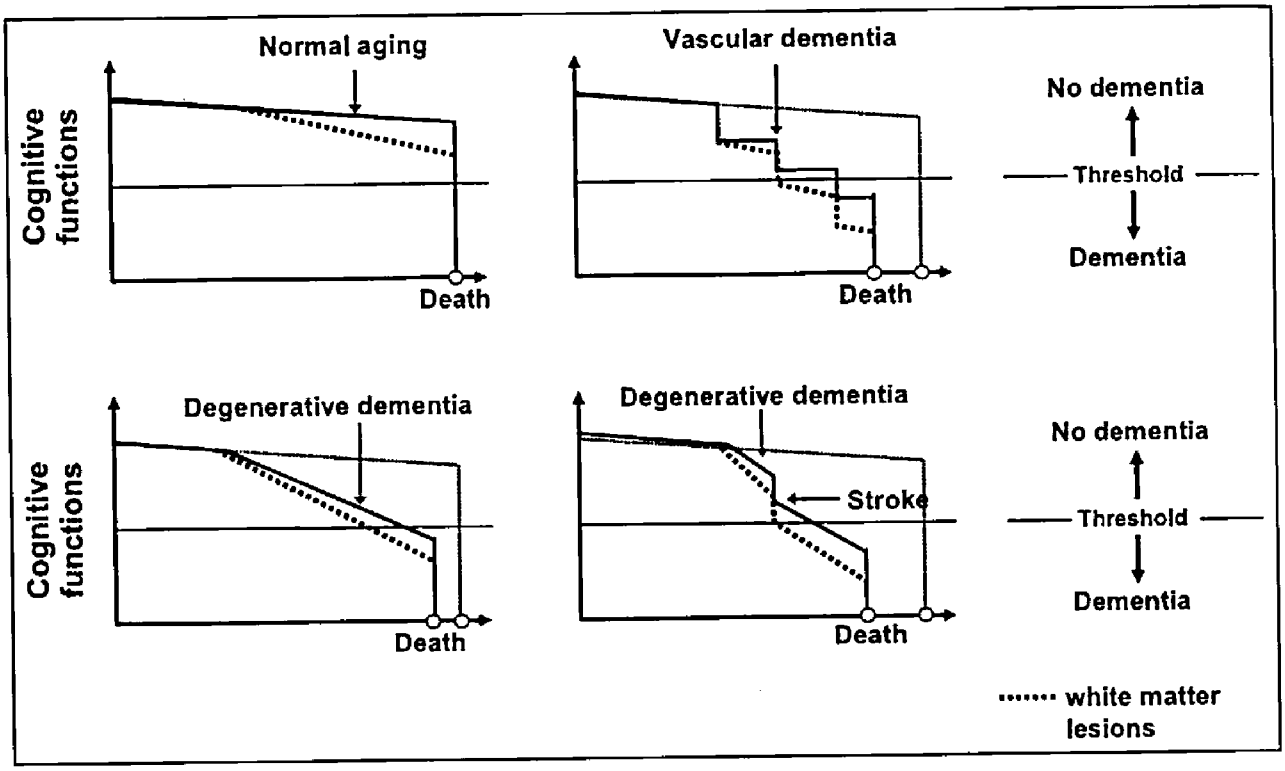

Figure 1. Time course of cognitive functions (reproduced with permission from reference 14).

Four years after two independent groups first reported an independent association between AD and the apolipoprotein E (*APOE*) ε4 allele [34,35] a quantitative overview of the literature, [36] published in 1997, and later studies [37] confirmed that the APOE ε4 allele represents a major risk factor for AD in all ethnic groups, across all ages between 40 and 90 years, and in both women and men. The ε4 allele enhances the risk threefold in heterozygotes and by a factor 15 in homozygotes [36]. The APOE ε4 allele accounts for most of the genetic risk in sporadic AD [2,6]. Here, the term sporadic is a misnomer, because late-onset AD is manifold more frequent than the familial forms of AD with onset at early age, which are due to mutations in APP or presenilin-1 [2,6].

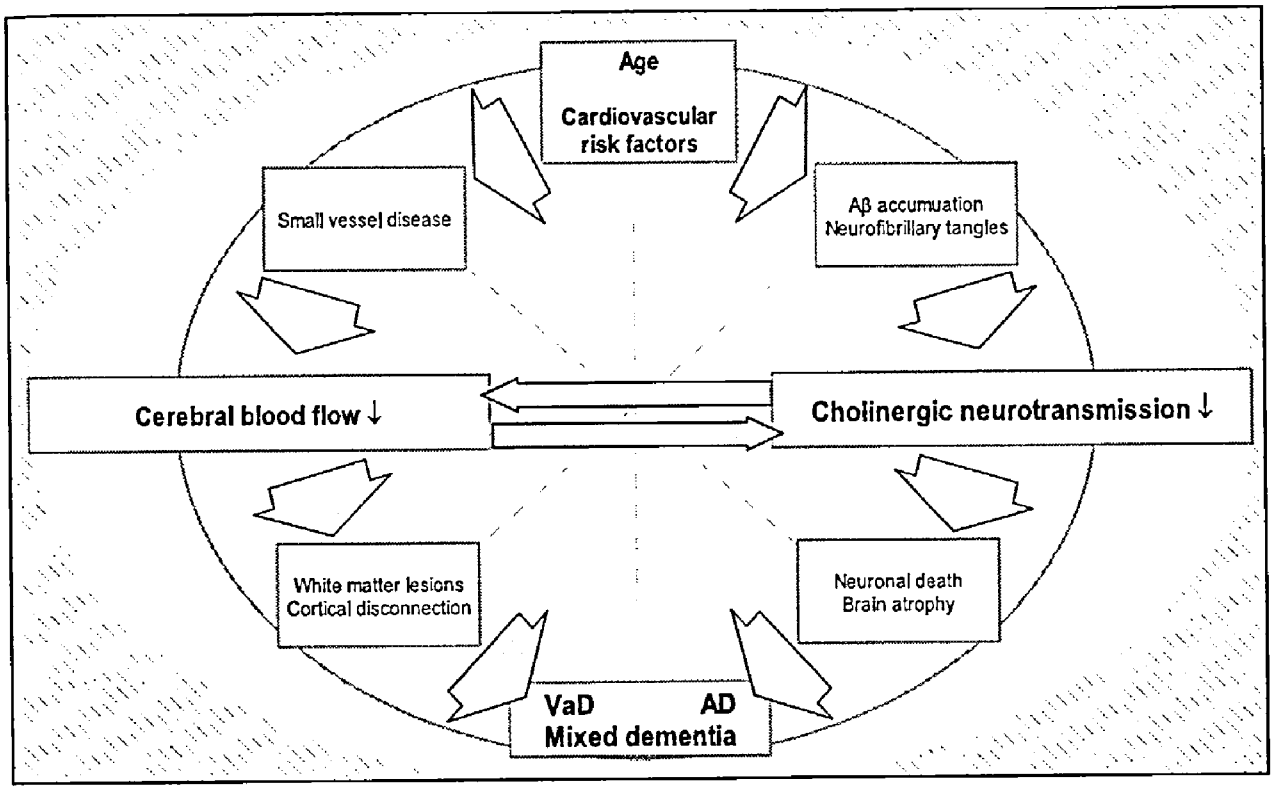

Figure 2. Overlap between neurodegenerative and vascular dementia and interaction between cholinergic factors and cerebral blood flow. Reproduced with permission from reference 9.

Blood Pressure as Risk Factor for Dementia

In middle-aged and older adults, hypertension is the predominant and most frequent cardiovascular risk factor. Any man normotensive at 50 years has a probability over 90% to become hypertensive during the remainder of his lifetime [40]. Studies on the association between cognition and blood pressure can be subdivided into those with a cross-sectional approach as opposed to those with a longitudinal design. The endpoint in these studies can be: disease outcomes, such as dementia, AD or VaD; morphologic or functional alterations of the brain as documented by modern neuroimaging techniques or histopathologic autopsy studies and cognitive function as assessed by batteries of tests each covering varying cognitive domains or more global tests of cognition, such as the Mini Mental State Examination (MMSE) or composite scores of specific tests.

Cross-Sectional Studies

Cross-sectional studies, in which outcome and exposure are simultaneously recorded, obviously have limited capability to assess the association between cognition and blood pressure. The extensive lag phase between the onset of hypertension and subsequent cognitive impairment together with the insidious clinical course of neurodegenerative dementia necessitate long-term prospective studies.

Longitudinal Cohort Studies

In 1996, Skoog and colleagues published a pioneering longitudinal study on the incidence of dementia in relation to blood pressure [42]. They recruited 70-year old residents (57.8% women) of Göteborg, Sweden, of whom 302, 205, and 94 were available for a re-assessment at 75, 79, and 85 years, respectively. Participants who developed dementia at age 79–85 had higher systolic blood pressure at 70 years (178 versus 164 mm Hg) and higher diastolic blood pressure at ages 70 (101 versus 92 mm Hg and 75 (97 versus 90 mm Hg) [42]. Patients specifically developing AD or VaD, had higher diastolic blood pressure at ages 70 and 75, respectively [42].

Although based on relatively few subjects, Skoog's seminal report [42] set the stage for subsequent studies published in the second half of the 1990s [43-46]. These reports confirmed that with multivariate adjustments a relatively high diastolic blood pressure (≥75 mm Hg versus ≤70 mm Hg) at age 50, [43] or a persistently elevated systolic blood pressure (≥140 mm Hg) at ages ranging from 43 [45] to 75 [44] years, or stage 2 hypertension (≥160 mm Hg systolic and ≥95 mm Hg diastolic) within the 59–71 age bracket [46] consistently predicted worse cognitive performance [43-46] or more severe white-matter lesions [45] at ages ranging from 63 [46] to 79 [45] years.

The clinical manifestations of the dementia syndrome cover a wide spectrum. Screening relies on tests of specific aspects of cognition or on global tests, such as the MMSE or composite scores of specific tests. By definition, the temporal association of cognitive decline or overt dementia with blood pressure is bound to be complex and not necessarily linear [41]. Coincident positive risk factors, such as age, a history of stroke, [47] or the number of *APOE* ε4 alleles, [48] as well as protective characteristics, such as a larger brain volume, [49] male sex, [50] moderate alcohol intake, [50] or education [50] modify the risk associated with blood pressure.

To clarify the role of blood pressure in the pathogenesis of cognitive impairment, we performed a systematic review of the prospective studies published since 2000, from which we extracted or computed summary statistics. The outcome variables were either levels of or changes in single or composite cognitive scores (Table 1), [51-62] the incidence of cognitive dysfunction, dementia, AD or VaD (Table 2), [38-40,47,48,57,63-71] or the appearance of brain lesions in histopathologic or neuroimaging studies (Table 3) [72-75]. For each of these 3 endpoints, we arranged the reports according to the age at enrolment.

TABLE 1 (starts). Association Between Cognitive Function and Blood Pressure Indexes

Study	Out-come	N	FU, y	Age, y	F, %	CVA, %	BP, mm Hg	Covariates	Effect size (95% confidence interval)	*P*
MLSH, 2004[51]	ΔV/FC	285	≈9.3	≈35	52	0	134/86 (56)	S, A, BMI, SMK, ALC, OCC, ED, DPR, PSM	[SP] –0.05 (–0.11 to 0.01) [DP] –0.09 (–0.19 to –0.00) [HT] –0.16 (–0.28 to –0.03)	≈0.13 ≈0.04 ≈0.01
Uppsala, 2000[52]	DS VF	463	20	50	0	0	≈131/83 (...)	A, DM, ED, OCC	[DP] ≈–1.00 (–1.90 to –0.10) [DP] ≈–0.32 (–0.65 to –0.03)	0.03 0.03
ARIC, 2001[53]	ΔDSS	10767	6.0	57	≈66		.../... (32)	C, R, A, ED, PSM	[HT] –0.40 (... to ...)	<0.05
ARIC, 2002[54]	ΔDSS	4928	6.0	≈57	≈52	0	120/72 (...)	R, A, DM, ED	[UHT] –0.90 (... to ...)	<0.05
MLSH, 2004[51]	ΔV/FC	244	≈9.3	58	51	0	152/91 (74)	S, A, BMI, SMK, ALC, OCC, ED, DPR, PSM	[SP] –0.09 (–0.14 to –0.03) [DP] –0.15 (–0.25 to –0.05) [HT] –0.24 (–0.39 to –0.08)	≈0.002 ≈0.002 ≈0.002
Framingham, 2003[55]	ΔSCCS	872 551	≈5.0	67 66	100 0	0 0	132/80 (...) 131/83 (...)	A, BMI, CHL, SMK, ALC, OCC, ED	[HT] –0.01 (–0.11 to –0.09) [HT] –0.16 (–0.30 to –0.02)	0.88 0.04
Malmö, 2003[56]	ΔSCCS	128	12.5	68	0	0	≈151/ 91 (16.7)	AHT, HD, PAD, DM, SMK, ALC, ED, MS, DPR	[HT2] 0.31 (0.11 to 0.51) [HT3] –0.31 (–0.54 to –0.07)	≈0.001 ≈0.01

TABLE 1 (continues). Association Between Cognitive Function and Blood Pressure Indexes

Study	Out-come	N	FU, y	Age, y	F, %	CVA, %	BP, mm Hg	Covariates	Effect size (95% confidence interval)	*P*
Clergy, 2006[57]	ΔSCCS	824	6.5	70	69	...	134/75 (52.0)	S, A, ED	[SP] –0.01 (–0.03 to 0.01) [DP] 0.00 (... to ...)	0.34 0.76
Duke EPESE, 2002[58]	ΔSPMS	3202	3.0	73	67	6.6	143/79 (52)	R, S, A, SMK, AHT, CVA, HD, DM, ED, DPR	[HT] 0.03 (–0.10 to 0.16)	0.68
Hispanic EPESE, 2005[59]	ΔMMSE	1138 (NT)	≈7.0	73	...	4.0	124/75 (0)	S, A, BMI, ΔBMI, CVA, CVD, DM, ΔAHT, SMK, ALC, PA, ED, INC	[SP] 0.80 (–0.38 to 1.98) [ΔSP] –0.08 (–0.14 to –0.02)	≈0.18 ≈0.008
		1721 (HT)	≈7.0	73	...	7.0	142/84 (100)		[SP] –0.10 (–0.49 to 0.29) [ΔSP] 0.01 (–0.30 to 0.32)	≈0.62 ≈0.95
Chicago, 2004[60]	ΔSCCS	4284	5.3	74	62	16.0	140/77 (...)	R, S, A, BPB, ED, FU	[ΔSP] –0.00 (–0.00 to 0.00) [ΔDP] –0.00 (–0.00 to 0.00)	0.30 0.70
ACTIVE, 2005[61]	ΔCSR	2017	1.0	74	76	7.0	.../... (≈41)	R, S, A, BMI, CHL, CVA, HD, DM, SMK, RIG, ED	[SH1] –0.18 (–0.34 to –0.02) [SH2] –0.28 (–0.48 to –0.09)	0.03 0.005
OCTO, 2004[62]	ΔMMSE	258	≈6.0	≈83	≈70	10.4	160/83 (44)	S, A, SMK, HD, CVA, ED, CTB	[HT] –0.54 (–1.13 to 0.05)	≈0.07

Abbreviations: *N*=number of subjects; *FU*=average follow-up; *F*=proportion of women; *CVA*=patients with stroke; and *BP*=average blood pressure at baseline (percentage of hypertensive patients). "≈" indicates estimates derived from the total study population and taken as representative for a subgroup, statistics computed from reported data, or *P*-values computed by a normal approximation from the confidence interval. "..." represents unreported information that could not be estimated. Studies were ordered according to age at enrolment.

Acronyms: *ACTIVE*=Advanced Cognitive Training for Independent and Vital Elderly; *ARIC*=Atherosclerosis Risk in Community; *EPESE*=Established Populations for Epidemiologic Studies of the Elderly; *MLSH*=Maine-Syracuse Longitudinal Study of Hypertension; and *OCTO*=Origins of variance in the Old-Old.

Endpoints: *ΔCSR*=changes in the composite of 3 test scores reflecting reasoning; *DS*=digit span test score; *ΔDSS*=difference in change over time in the Digit Symbol Subtest of the Wechsler Adult Intelligence Test (Revised) compared to normotensive subjects; *ΔMMSE*=estimated change in the Mini Mental State Examination score over the whole follow-up period; *ΔSCCS*=annual change in standardized composite cognitive score; *ΔSPMS*=3-year change in score obtained by Short Portable Mental Status questionnaire; *ΔVIFC*=annual change in the Visualization/Fluid Composite score as derived from the Wechsler Adult Intelligence Test; and *VF*=verbal fluency test score.

Covariates: *A*=age; *AHT*=antihypertensive drug treatment; *ΔAHT*=institution of antihypertensive treatment; *ALC*=alcohol intake; *BMI*=body mass index; *ΔBMI*=change in body mass index; *BPB*=blood pressure at baseline; *C*=center; *CHL*=hypercholesterolemia or serum cholesterol; *CTB*=cognitive tests at baseline; *CVA*=stroke; *DM*=diabetes mellitus; *DPR*=depression; *ED*=education; *FU*=follow-up duration; *HD*=heart disease; *INC*=income; *MS*=marital status; *OCC*=occupation; *PA*=physical activity; *PAD*=history of peripheral artery disease; *PSM*=psychotropic medication; *R*=race; *RIG*=randomized intervention group; *S*=sex; and *SMK*=smoking.

Blood pressure indexes at baseline: *DP/SP*=diastolic (+5 mm Hg)/systolic (+10 mm Hg) blood pressure; *ΔDP/ ΔSP*=change from baseline in diastolic/systolic blood pressure (+1 mm Hg); *HT*= hypertension; *HT2/HT3*=stage 2/3 hypertension; and *UHT*=uncontrolled hypertension.

Effect size: score of cognitive test or change in test score associated with blood pressure indexes on a continuous or categorical scale.

All studies of cognitive function, involving subjects on average less than 70 years old at enrollment (Table 1), [51-56] uniformly showed a significantly lower performance or a more rapid decline of cognitive function with higher blood pressure, although in one cohort only for stage 3 hypertension [56]. At more advanced age, [57-62] point estimates went in the same direction, but only reached significance in the normotensive Hispanic EPESE (Established Populations for Epidemiologic Studies of the Elderly) cohort [59] and in the ACTIVE (Active Cognitive Training Independent and Vital Elderly) trial [61].

Among the studies with cognitive impairment as a categorical endpoint (Table 2) [38-40,47,48,57,63-71], those using a dichotomized test score [46,47] classified from 15% [48] to 50% [47] of the participants as cognitively impaired and reported positive associations with hypertension. Two studies [64,68] found no association of MCI with hypertension earlier in life. Studies with dementia, [38,40,66] AD, [39,40,57,63,65-67,69-71] or VaD [63,66,70] as endpoints demonstrated a significantly positive association with one or more blood pressure indexes, if follow-up started from middle age rather than old age [38,40,65,66]. Remarkably, one study involving subjects recruited at the upper end of the age spectrum found an inverse association of AD with blood pressure [67]. In keeping with the estimates listed in Table 2, the Baltimore Longitudinal Survey of Aging, based on 11 years of multivariate adjusted follow-up of 847 subjects (mean age, 70.6 years; 41% women) described age as an important modifier of the effects of blood pressure on cognition [41]. Among younger participants (60 years at baseline), those with higher systolic blood pressure performed worse on tests of nonverbal memory and confronting naming, although the test results improved over time due to a learning effect [41]. Among older participants (80 years), those with higher systolic blood pressure not only performed worse than subjects with normal blood pressure, but also experienced a decline in cognitive performance over time [41].

In summary, our overview suggests that especially hypertension in middle age adversely affects cognition later in life. In old and very old adults, the association between impaired cognition and hypertension becomes weaker and more difficult to demonstrate, perhaps because in prospective population studies diastolic blood pressure decreases after age 50, [76] or because systolic blood pressure falls in the very old [42]. Finally, 1 autopsy report [72] and 3 brain imaging studies [73-75] with longitudinal perspective observed independent and positive associations between brain lesions and blood pressure indexes (Table 3).

Low Blood Pressure as Manifestation of Dementia

Already in 1996, Skoog noticed that with advancing age all subjects in his study experienced a decrease in blood pressure, but that the fall in systolic and diastolic blood pressure was greater in patients who developed dementia than in their nondemented counterparts [42]. A retrospective review of the medical records of 1133 women (≥75 years) covering 10 years [77] revealed that systolic blood pressure increased with time in 568 unimpaired subjects, but that it increased less in 274 and 291 women who either developed cognitive impairment or became demented. Diastolic blood pressure declined significantly with time in all 3 groups [77]. In a cohort of 242 French patients with moderate AD (mean age, 78 years; 74% women) [78] blood pressure significantly fell over 1 year of follow-up, independently of sex, age, body mass index, and antihypertensive drug therapy.

Progressive physical inactivity in those blemished by advancing mental deterioration may be a substantial factor leading to a fall in blood pressure in the years immediately preceding and following overt dementia. In addition, neuronal death and defective cholinergic neurotransmission affecting the autonomic centers in the brain probably results in a dysregulation of blood pressure (Figure 2). Orthostatic or postprandial dips in blood

pressure, pari passu with episodes of impaired cerebrovascular blood flow, might actually contribute to further brain damage, sustaining a perpetuating vicious circle [79].

Reversibility of Risk Associated with Hypertension

Nonrandomized prospective studies and randomized clinical trials explored to what extent blood pressure lowering drugs might affect the risk of cognitive impairment or frank dementia.

Nonrandomized Observational Studies

Ten prospective studies (Table 4) [46,80-88] explored in multivariate-adjusted analyses the possible influence of antihypertensive treatment on the incidence of cognitive impairment or overt dementia. Differences in the definition of the cognitive endpoint, the wide range of age at baseline and consequent duration of follow-up, varying sampling frames, and adjustment for different sets of covariates or effect modifiers, such as the *APOE* ε4 polymorphism [46,88], turned the computation of a pooled association size into a mission impossible. Nevertheless, of the 10 studies (Table 4) [46,80-88], 8 reported that antihypertensive drug treatment lowered the risk of cognitive decline, the reduction being significant in 5 reports [80,81,84,86,87]. No single study observed a multivariate-adjusted significantly elevated risk in treated hypertensive patients. Several researchers tried to dissect the correlation between cognitive impairment and antihypertensive treatment according to the main classes of antihypertensive drugs (Table 4). Although plagued by low numbers and overexploitation of scarce data, the mainstream of these analyses suggests that diuretics [80,87] might confer particular benefit in the prevention of cognitive impairment. Two observational studies [89,90] suggested that calcium channel blockers might adversely affect cognition, but probably reflected reverse causality, patients with more severe hypertension being more likely to be treated with this potent drug class, self-selection of patients consenting to follow-up, and the arbitrary nonrandomized definition of the drug class used as reference [89]. These reports have to be viewed within the context of the controversy in former times, blaming calcium channel blockers for a wide range of adverse reactions, of which none withstood the test of randomized controlled trials [91].

Nonrandomized longitudinal studies of cognitive function have to be interpreted within the context of their well-known methodological limitations. Randomized controlled trials with a double-blind design and a predefined plan of statistical analysis protect against most of these weaknesses. Single-blind protocols or open administration of treatment with blinded endpoint evaluation [92] remove bias in the validation of events, but not in the reporting of events.

TABLE 2 (starts). Association Between Risk of Dementia and Blood Pressure Indexes

Study	Out-come	N	Events (rate per 100)	FU, y	Age, y	F, %	CVA, %	BP, mm Hg	Covariates	Relative risk (95% confidence interval)	*P*
KPNC, 2005[38]	DEM	8845	721 (8.2)	26.7	42	54	...	.../... (19)	R, S, A, ED	[HT] 1.24 (1.04 to 1.48)	≈0.01
Hiroshima, 2003[63]	VaD	1774	38 (2.1)	≈27	≈44	73	...	117/... (...)	S, A, MLK, ED	[SP] 1.33 (1.14 to 1.56)	<0.001
	AD		51 (2.9)						S, A, DM	[SP] ... (... to ...)	>0.05
North Karelia, 2001[64]	MCI	1409	82 (5.8)	20.9	50	62	...	144/89 (...)	A, BMI	[SH1] 0.8 (0.4 to 1.3)	≈0.36
										[SH2] 1.2 (0.7 to 2.2)	≈0.55
										[DH1] 0.9 (0.5 to 1.7)	≈0.74
										[DH2] 1.1 (0.7 to 1.9)	≈0.73
North Karelia, 2001[65]	AD	1409	48 (3.4)	20.9	50	62	...	144/89 (...)	A, BMI, SMK,	[SH1] 2.1 (0.8 to 5.0)	≈0.09
									ALC, CVA, HD,	[SH2] 2.8 (0.1 to 7.2)	≈0.03
									ED	[DH1] 1.4 (0.6 to 3.5)	≈0.46
										[DH2] 1.7 (0.8 to 3.6)	≈0.16
CAIDE, 2005[40]	DEM	1409	... (5.8)	21.0	50	62	7.2	144/89 (...)	S, A, BMI, CHL,	[SH] 1.97 (1.03 to 3.77)	≈0.04
	AD		... (3.8)						ED, FU	[SH] 1.57 (0.78 to 3.14)	≈0.19
HAAS, 2001[48]	CASI	3605	539 (15.0)	26.0	52	0	6.2	132/82 (...)	A, BMI, SMK,	[SH2–E4] 1.8 (1.2 to 2.9)	≈0.01
									ALC, ED	[SH2+E4] 2.9 (1.4 to 6.3)	≈0.006

TABLE 2 (continues). Association Between Risk of Dementia and Blood Pressure Indexes

Study	Out-come	N	Events (rate per 100)	FU, y	Age, y	F, %	CVA, %	BP, mm Hg	Covariates	Relative risk (95% confidence interval)	*P*
HAAS, 2000[67]	DEM	3703	197 (5.3)	27.0	53	0	6.3	131/83 (≈33)	A, SMK, ALC, E4, CVA, HD, PAD, ED	[SH1–T] 1.15 (0.62 to 2.13)	≈0.65
										[SH2–T] 3.88 (1.50 to 10.0)	≈0.004
										[DH1–T] 3.78 (1.59 to 8.95)	≈0.002
										[DH2–T] 4.00 (1.56 to 10.2)	≈0.003
	AD	3703	118 (3.2)							[SH1–T] 1.23 (0.63 to 2.43)	≈0.54
										[SH2–T] 1.22 (0.37 to 4.04)	≈ 0.74
										[DH1–T] 3.49 (1.28 to 9.52)	≈0.01
										[DH2–T] 4.47 (1.53 to 13.1)	≈0.005
	VaD	3703	79 (2.1)							[SH1–T] 0.81 (0.21 to 3.19)	≈0.76
										[SH2–T] 11.8 (3.52 to 39.5)	<0.001
										[DH1–T] 3.45 (0.79 to 15.0)	≈0.09
										[DH2–T] 2.49 (0.46 to 13.4)	≈0.28
Rotterdam and Gothenburg, 2001[67]	AD	4987	25 (0.5)	2.1	65	57	...	137/74 (...)	C, S, A, AHT, CVA, HD, DM, ED, CTB	[SP] 0.96 (0.80 to 1.16)	≈0.67
										[DP] 0.95 (0.81 to 1.15)	≈0.68
Clergy members, 2006[57]	AD	824	151 (18.3)	6.5	70	69	...	134/75 (52.0)	S, A, ED	[SP] 0.95 (0.82 to 1.04)	0.25
										[DP] 1.00 (0.93 to 1.08)	0.98
ILSA, 2004[68]	MCI	1445	105 (7.3)	3.5	72	56	5.7	.../... (69)	A, SMK, HD, ED	[HT] 1.20 (0.76 to 1.89)	≈0.42

TABLE 2 (continues). Association Between Risk of Dementia and Blood Pressure Indexes

Study	Out-come	N	Events (rate per 100)	FU, y	Age, y	F, %	CVA, %	BP, mm Hg	Covariates	Relative risk (95% confidence interval)	*P*
SOF, 2005[47]	TB	6306	≈6150 (50.0)	≈6.8	≈72	100	≈0	.../... (...)	A, CTB, FU	[HT–IS] 1.13 (1.04 to 1.22)	0.002
KAME Project, 2005[69]	AD	1859	90 (4.8)	6.0	73	56		≈140/ 74 (≈33.5)	E4	[SH] 1.79 (0.82 to 3.89)	0.15
SOF, 2005[47]	TB	119	76 (63.9)	8.7	75	100	0.8	148/78 (...)	A, CTB, FU	[HT+IS] 4.07 (1.37 to 12.1)	0.01
Manhattan, 2002[70]	AD VaD	1259	157 (12.5) 56 (4.4)	7.0	76	69	12.5	.../... ()	R, S, A, HD	[HT] 0.8 (0.6 to 1.1) [HT] 1.6 (0.9 to 2.9)	≈0.16 ≈0.11
Luchsinger, 2005[110]	AD	1012	246 (24.3)	≈5.5	≈76	≈70	...	.../... (≈49)	R, S, A, E4, ED	[HT] 1.5 (0.9 to 2.1)	≈0.08
CHCS, 2003[71]	DEM	2939	480 (16.3)	≈5.0	≈76	≈59	≈4.6	.../... (≈44)	R, S, A, E4, CVA, HD, DM, ED, CTB, MRI	[HT] 1.00 (0.94 to 1.27)	≈0.99
Rotterdam and Gothenburg, 2001[67]	AD	1336	68 (5.1)	2.1	79	65	...	146/72 (...)	C, S, A, AHT, CVA, HD, DM, ED, CTB	[SP] 0.95 (0.85 to 1.06) [DP] 0.98 (0.88 to 1.08)	≈0.35 ≈0.61
Rotterdam and Gothenburg, 2001[67]	AD	662	103 (15.6)	2.1	87	74	...	155/73 (...)	C, S, A, AHT, CVA, HD, DM, ED, CTB	[SP] 0.89 (0.82 to 0.97) [DP] 0.91 (0.84 to 0.98)	≈0.007 <0.001

Abbreviations: N=number of subjects; FU=average follow-up; F=proportion of women; CVA=patients with stroke; BP=average blood pressure at baseline (percentage of hypertensive patients). "≈" indicates estimates derived from the total study population and taken as representative for a subgroup, statistics computed from reported data, or *P*-values computed by a normal approximation from the confidence interval. "..." represents unavailable information that could not be estimated. Studies were ordered according to age at enrolment.

Acronyms: *CAIDE*=Cardiovascular Risk Factors, Aging and Dementia Study; *CHCS*=Cardiovascular Health Cognition Study; *HAAS*=Honolulu Asia Aging Study; *ILSA*=Italian Longitudinal Study on Aging; *KAME*=prospective study of Japanese Americans living in King County, WA; *KPNC*=Kaiser Permanente of Northern California; and *SOF*=Study of Osteoporotic Fractures

Endpoints: *AD*=Alzheimer disease; *CASI*=Cognitive Abilities Screening Instrument score below 15th percentile; *DEM*=dementia; *MCI*=mild cognitive impairment; *TB*=larger than median decrease in Trail B test score; and *VaD*=vascular dementia.

Covariates: *A*=age; *AHT*=antihypertensive drug treatment; *ALC*=alcohol intake; *BMI*=body mass index; *C*=cohort; *CHL*=hypercholesterolemia or serum cholesterol; *CTB*=cognitive tests at baseline; *CVA*=history of stroke; *DM*=diabetes mellitus; *E4*=number of *APOE* ε4 alleles; *ED*=education; *FU*=follow-up duration; *HD*=history of heart disease; *MRI*=brain lesions identified by magnetic resonance imaging at baseline; *MLK*=milk intake; *PAD*=history of peripheral artery disease; *R*=race; *S*=sex; and *SMK*=smoking.

Blood pressure indexes at baseline: *DP/SP*=diastolic (+5 mm Hg)/systolic (+10 mm Hg) blood pressure; *DH1/DH2*=diastolic blood pressure 90–94 mm Hg/≥95 mm Hg; *DH1–T/ DH2–T*=diastolic blood pressure 90–94/≥95 mm Hg in the absence of antihypertensive treatment; *HT*= hypertension; *HT–IS/HT+IS*=hypertension without/with intervening stroke; *SH*=systolic hypertension; *SH1/HT2*=stage 1/2 systolic hypertension; *SH1–T/SH2–T*=stage 1/2 systolic hypertension in the absence of treatment; and *SH2–E4/ SH2+E4*=stage 2 systolic hypertension in absence/presence of the *APOE* ε4 allele.

The trial conducted by the Medical Research Council (MRC) in older adults [93] was the first outcome study that investigated the effects of antihypertensive drug treatment on cognitive function. The patients were randomized to a diuretic, (hydrochlorothiazide plus amiloride), a β-blocker (atenolol), or placebo [93]. Both active treatments reduced blood pressure below the placebo level. Over a period of 54 months, 2584 patients underwent elaborate psychometric tests [93]. No significant differences in the test scores occurred. However, follow-up of 387 surviving MRC patients for 9–12 years revealed that less decline in systolic blood pressure led to a poorer cognitive outcome, even with adjustments applied for a family history of dementia, cognitive function at baseline, increasing age, and alcohol intake [94]. Many other randomized clinical trials of short duration with small sample size that focused on single or composite cognitive scores, primarily served the marketing goals of newer classes of antihypertensive drugs [95,96], and can at best be viewed as hypothesis generating.

The MRC study [93], unfortunately, did not report on the incidence of overt dementia. In 4 outcome trials of blood pressure lowering treatment, [97-100] dementia was a secondary outcome in its own right. The double-blind placebo-controlled Systolic Hypertension in the Elderly Program [97] included 4736 patients with mean age of 72 years. SHEP failed to demonstrate a significant effect of antihypertensive treatment on the incidence of dementia (Figure 3) despite between-group blood pressure differences exceeding 10 mm Hg systolic and 4 mm Hg diastolic. The rates on placebo and active treatment were 4.2 and 3.6 cases per 1000 patient-years (relative risk reduction [RRR], 14%; 95% confidence interval [CI], –26 to 54%; P=0.44) [97]. Active treatment consisted of chlorthalidone with the possible addition of atenolol or reserpine. A subsequent report [101] noticed that although retention to the clinical examinations was very high, SHEP patients who missed cognitive assessments were more likely to be older, less educated, non-White, randomized to placebo, and to have a higher occurrence of nonfatal cardiovascular events before each follow-up visit. The interpretation was that selective attrition might have biased the SHEP dementia results towards the null hypothesis of no differences between the treatment groups [101].

In the double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial, active treatment consisted of the dihydropyridine calcium-channel blocker nitrendipine, which could be combined with enalapril, hydrochlorothiazide, or both add-on drugs, to achieve blood pressure control [102]. Median follow-up lasted only 2 years. The trial had to be stopped prematurely, because active treatment resulted in a 42% decrease in the primary endpoint of fatal and nonfatal stroke [102]. Of 4695 randomized patients, 2418 participated in the substudy on dementia (mean age, 70 years). Compared with placebo, active treatment reduced blood pressure by 8.3 mm Hg systolic and 3.8 mm Hg diastolic and reduced the incidence of dementia by 50% from 7.7 to 3.8 cases per 1000 patient-years [103]. After the double-blind trial had stopped in 1997, all patients were offered therapy with the same active medication. Median follow-up lengthened to 3.9 years. The number of dementia cases doubled from 32 to 64 (41 with Alzheimer's disease) [98]. Immediate compared to delayed antihypertensive therapy reduced the risk of dementia by 55% (CI, 24 to 73%; P<0.001) from 7.4 to 3.3 cases per 1000 patient-years (Figure 3) [98].

TABLE 3. Association Between Brain Lesion and Blood Pressure Indexes

Study	Out-come	N	FU, y	Age, y	F, %	CVA, %	BP, mm Hg	Covariates	Effect size (95% confidence interval)	*P*
HAAS, 2000[72]	NFTH	243	36.0	53	0	(...)	.../... (...)	A (at death), E4, AHT	[SH2] 1.41 (0.73 to 2.74)	≈0.30
									[DH2] 2.39 (1.34 to 4.26)	≈0.003
	NFTN								[SH2] 1.51 (0.60 to 3.79)	≈0.37
									[DH2] 1.66 (0.67 to 4.10)	≈0.26
	NPH								[SH2] 2.18 (1.07 to 4.46)	≈0.03
									[DH2] 0.87 (0.31 to 2.45)	≈0.79
	NPN								[SH2] 2.05 (1.00 to 4.20)	≈0.05
									[DH2] 0.69 (0.24 to 1.98)	≈0.48
Zoetermeer, 2002[73]	WMLS	514	≈20	51	53	...	131/81 (25)	S, A, BMI, SMK, DM	[HT<20] 2.9 (1.5 to 5.8)	≈0.002
									[HT>20] 2.6 (1.2 to 5.6)	≈0.01
Rotterdam, 2002[73]	WMLS	563	≈5	69	50	...	137/73 (39)	S, A, BMI, SMK, DM	[HT<5] 1.6 (0.9 to 2.9)	≈0.11
									[HT>5] 1.8 (1.1 to 3.0)	≈0.02
Rotterdam, 2003[74]	CAS	434	20	51	53	...	131/81 (...)	S, A, SMK	[DP–T] 0.08 (0.00 to 0.17)	≈0.05
		79							[DP+T] –0.02 (–0.22 to 0.19)	≈0.89
Goldstein, 2005[75]	WMH	121	5.0	66	57	0	119/72 (0)	A	[SP] 1.49 (1.10 to 2.02)	0.01
									[SPA] 1.57 (1.08 to ≈1.70)	0.02

Abbreviations: *N*=number of subjects; *FU*=average follow-up; *F*=proportion of women; *CVA*=patients with stroke; and *BP*=average blood pressure at baseline (percentage of hypertensive patients). "≈" indicates *P*-values computed by a normal approximation from the confidence interval. "..." represents unavailable information that could not be estimated. Studies were ordered according to age at enrolment.

Study acronym: *HAAS*=Honolulu Asia Aging Study.

Endpoint: *CAS*=cortical atrophy score on magnetic resonance imaging of the brain; *NFTH/NFTN*=count ratio versus normal blood pressure for neurofibrillary tangles in hippocampus/neocortex; *NPH/NPN* =count ratio versus normal blood pressure for neuritic plaques in hippocampus/neocortex; *WMH*=white-matter hyperintensities; and *WMLS*=subcortical white matter lesions defined as the upper fifth of the distribution according to severity.

Covariates: *A*=age; *AHT*=antihypertensive drug treatment; *BMI*=body mass index; *DM*=diabetes mellitus; *E4*=number of *APOE* ε4 alleles; *S*=sex; and *SMK*=smoking.

Blood pressure indexes at baseline: *DH2*=diastolic blood pressure ≥95 mm Hg; DP=diastolic blood pressure (+5 mm Hg); *DP–T/ DP+T*=diastolic blood pressure (+5 mm Hg) in the absence/presence of antihypertensive treatment; HT<5/HT<20=hypertension present for less than 5/20 years; *HT>5,HT>20*=hypertension present for more than 5 or 20 years; *SH2*=stage 2 systolic hypertension; *SP*=systolic blood pressure (+ 10 mm Hg); and *SPA*=systolic blood pressure on daytime ambulatory measurement (+10 mm Hg).

Effect size: relative risk associated with exposure variable except for CAS, for which the difference associated with a 5 mm Hg higher diastolic blood pressure at baseline is given.

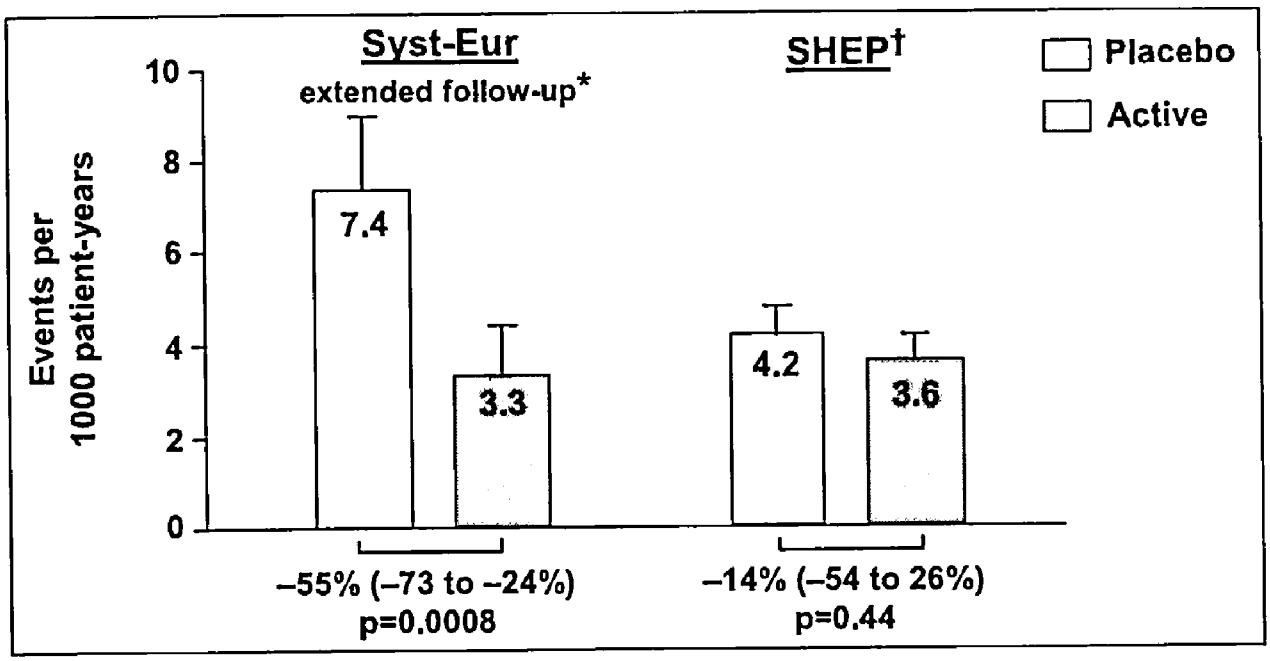

Figure 3. Incidence of dementia in the Systolic Hypertension in Europe trial (Syst-Eur132) and the Systolic Hypertension in the Elderly Program (SHEP131). In the Syst-Eur trial, the number of cases of new-onset Alzheimer disease was 29/43 and 12/21 in the patients randomized to placebo and active treatment, respectively.132 The corresponding incidence of vascular dementia was 12/43 and 7/21.132 The SHEP reports131,135 did not differentiate between Alzheimer disease and vascular dementia. Reproduced with permission from reference 9.

In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [99], combination therapy with perindopril plus indapamide (RRR, 23%; CI, 0 to 41%, P=0.05), but not monotherapy with perindopril alone (RRR –8%; CI –48 to 21%, P=0.60), compared to placebo, reduced the incidence of dementia in 6105 patients with pre-existing cerebrovascular disease (mean age, 64 years). The systolic/diastolic blood pressure differences averaged 12/5 mm Hg and 5/3 mm Hg in the combination therapy and monotherapy arms, respectively. There was no apparent effect of active treatment among participants (16.4%) with evidence of cognitive impairment at baseline (RRR, –5%; CI, –42 to 22%; P=0.70), whereas among patients without such impairment (84.2%) active treatment protected against poststroke dementia (RRR, 31%; CI, 6 to 49%; P=0.02) [99].

The Study on Cognition and Prognosis in the Elderly (SCOPE) was set up as a double-blind placebo-controlled trial in 4964 patients (mean age, 76 years) [100]. However, open-label antihypertensive drugs, which mainly consisted of diuretics, β-blockers, or both classes of old drugs, were added to the double-blind study medication in a considerably greater proportion of the patients randomized to placebo than in those allocated candesartan [100]. The achieved blood pressure was 3.2/1.6 mm Hg lower in the candesartan group. In a post-hoc analysis [104], patients with cognitive impairment at baseline (MMSE score, 24 to 28) experienced less further decline in this test on candesartan than in the control group.

Overall, the 4 dementia trials [97-100] included 18 196 patients and 642 dementia cases. The P-value for heterogeneity across trials was not significant (P=0.18) [105]. Based on a fixed-effects model, the pooled odds ratio for the prevention of dementia was 0.89 (CI, 0.75 to 1.04) and did not reach statistical significance (P =0.15) [105]. However, sensitivity analyses revealed a difference in the pooled odds ratios, depending on whether active

treatment started with an inhibitor of the renin system or not (Figure 4). The pooled odds ratios were 0.75 (CI, 0.60 to 0.94; P = 0.01) for SHEP [97], Syst-Eur [98] and the combination therapy subgroup of PROGRESS [106] and 1.08 (CI, 0.84 to 1.38; P =0.54) for SCOPE [100] and the perindopril-only subgroup of the PROGRESS trial [106]. The difference between the latter summary statistics was significant (P = 0.04) [105].

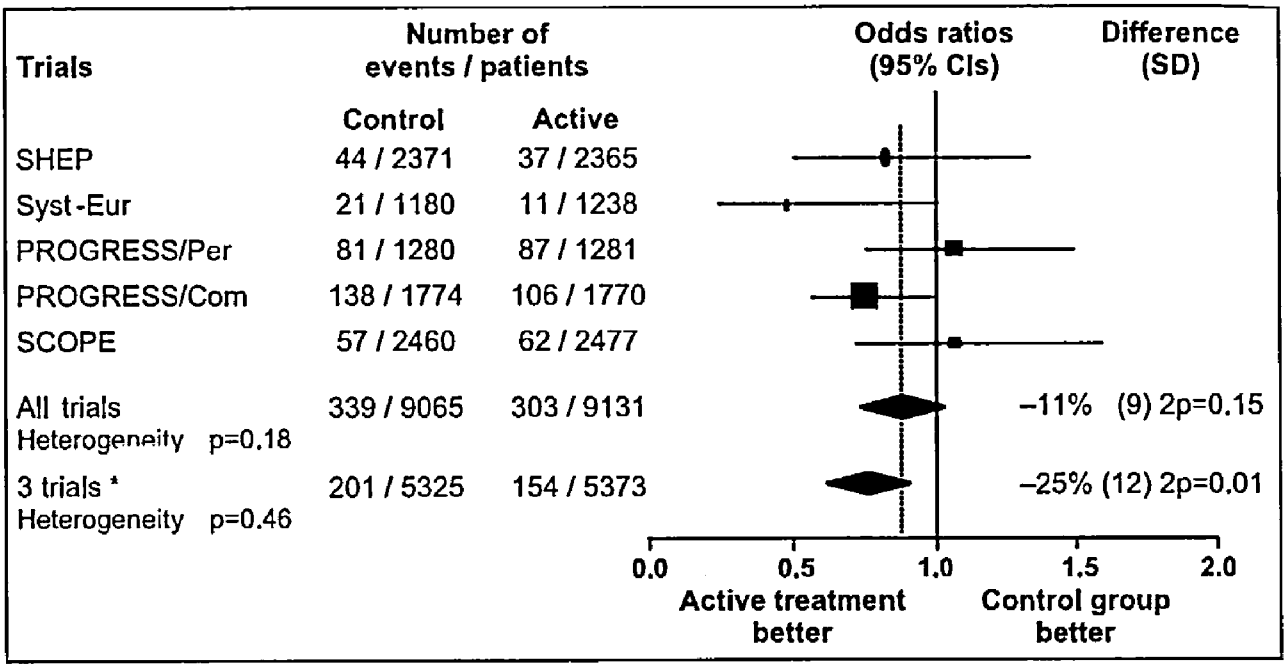

Figure 4. Effects of blood pressure lowering treatment on the incidence of dementia in placebo-controlled trials. Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of the variance of the odds ratios. Horizontal lines and diamonds denote the 95% confidence intervals for individual trials and summary statistics, respectively. Pooled estimates were computed from a fixed-effect model. The vertical dotted line marks the position of the point estimate of the pooled effect sizes for all trials combined and trials in which the active treatment included either a diuretic or a dihydropyridine calcium channel blocker. Reproduced with permission from reference 9.

Mechanism Underlying Prevention of Alzheimer Disease by Blood Pressure Lowering

The prevention of VaD or poststroke dementia by blood pressure lowering is in keeping with the well-known vascular origin of these conditions. Until now, Syst-Eur [102,103] remains the only trial that showed a significant decrease in the incidence of AD (Figure 3). At the time of the first Syst-Eur report [102], this was an unexpected observation. However, the subsequently published literature, as reviewed above, indicates that vascular factors, particularly hypertension, do play if not a causal then at least a permissive role in the pathogenesis of AD (Figure 2). On the other hand, for nearly the same blood pressure reduction, antihypertensive treatment with a thiazide did not protect against AD in the SHEP trial [97].

As we discussed elsewhere, several lines of evidence suggest that dihydropyridine calcium-channel blockers might specifically protect against neurodegeneration.

TABLE 4 (starts). Association Between Cognitive Impairment and Antihypertensive Drug Treatment in Nonrandomized Studies

Study	Out-come	N	Events (rate per 100)	FU, y	Age, y	F, %	CVA, %	Treated, %	Covariates	Effect size (95% confidence interval)	*P*
EVA, 1999[46]	CI	1150	98 (8.5)	4.0	65.2	58.8	...	25.6	S, A, E4, ALC, ED, MMSE, DPR	1.1 (0.7 – 1.7)	≈0.66
BLSA, 2005[85]	AD	1092	115 (10.5)	11.0	67.1	37.3	...	20.1 [C]	S, S/DBP, HD, SMK, ED	0.63 (0.31 – 1.28)	≈0.19
			6 [dC]					10.6 [Cd]		0.30 (0.07 – 1.25)	0.10
			12 [ndC]					13.0 [Cnd]		0.82 (0.37 – 1.83)	0.63
Kuopio, 2004[88]	MCI	747	66 (8.8)	3.2	≈67.8	≈61.2	≈11.1	≈33.9	S, A, E4, CVD, CVA, HT, DM, ED	1.61 (0.87 – 2.99)	≈0.12
Rotterdam, 2001[81]	DEM	6416	118 (1.8)	2.2	68.7	58.7	2.3	28.6	S, A, BMI, S/DBP, CVA, PAD, DM, SMK, ED, MMSE	0.67 (0.45 – 1.00)	≈0.046
	AD		82 (1.3)							0.77 (0.49 – 1.24)	≈0.25
	VaD		18 (0.3)							0.30 (0.09 – 0.92)	≈0.032
EPESE, 2001[82]	AD	634	99 (15.6)	4.0	72.0	63.2	4.1	33.6	S, A, SBP, SF, IS	0.66 (0.17 – 2.61)	≈0.54
								26.5 [D]		1.33 (0.68 – 2.61)	≈0.40
CSHA, 2002[83]	AD	3238	152 (4.7)	5.0	≈73.3	≈58.0	≈7.6	41.2	S, A, ED	0.91 (0.64 – 1.30)	≈0.74

TABLE 4 (continues). Association Between Cognitive Impairment and Antihypertensive Drug Treatment in Nonrandomized Studies

Study	Out-come	N	Events (rate per 100)	FU, y	Age, y	F, %	CVA, %	Treated, %	Covariates	Effect size (95% confidence interval)	*P*
CCS, 2006[87]	AD	3217	102 (3.17)	3.2	≈74.1	≈58.2	≈4.2	45.3	S, A, CHL, E4, CVA,	0.64 (0.41 – 0.98)	≈0.036
			26 [D]					26.5 [D]	HD, DM, ED	0.61 (0.37 – 0.98)	≈0.037
			5 [pD]					5.8 [Dp]		0.26 (0.08 – 0.64)	≈0.003
			14 [C]					14.9 [C]		0.86 (0.45 – 1.53)	≈0.60
			4 [dC]					5.8 [Cd]		0.53 (0.16 – 1.34)	≈0.17
			10 [ndC]					9.2 [Cnd]		1.16 (0.55 –2.20)	≈0.64
			15 [A]					13.0 [A]		1.13 (0.60 – 1.98)	≈0.66
PHRSP, 2005[86]	CI	350	62 (17.7)	2.1	76.9	73.0	≈6.6	≈54.4	R, S, A, BMI, BP, CHL, CVA, DM, SMK, ALC, MMSE, FHD	0.56 (0.38 – 0.83)	0.004
Indianapolis, 2002[84]	CI	1617	288 (17.8)	≈4.7	77.7	66.5	10.8	46.6	S, A, HD, HT, ED,	0.62 (0.45 – 0.84)	0.002
								28.3 [D]	CSID	0.80 (0.58 – 1.10)	0.17
								18.2 [C]		0.86 (0.60 – 1.25)	0.44
								11.1 [Cd]		0.94 (0.60 – 1.46)	0.78
								9.5 [A]		0.64 (0.38 – 1.09)	0.002
Kungsholmen, 1999[80]	DEM	1307	224 (17.1)	3.0	82.5	76.1	≈10.0	44.9	S, A, SBP, CVA, HD,	0.7 (0.6 – 1.0)	0.03
			73 [D]					37.0 [D]	ED	0.7 (0.5 – 1.0)	0.02

Abbreviations: *N*=number of subjects; *FU*=average follow-up; *F*=proportion of women; and *CVA*=patients with stroke. "≈" indicates estimates derived from the total study population and taken as representative for subgroup, statistics computed from reported data, or *P*-values computed by a normal approximation from the confidence interval. "..." represents unavailable information that could not be estimated. Studies were ordered according to age at enrolment.

Acronyms: *BLSA*=Baltimore Longitudinal Study on Aging; *CCS*=Cache County Study; *CSHA*=Canadian Study of Health and Aging; *EPESE*= Established Populations for Epidemiologic Studies of the Elderly; *EVA*=Epidemiology of Vascular Aging Study; and *PHRSP*=Palmetto Health Richland Senior Primary Care Practice

Antihypertensive drugs: *A*=angiotensin-converting enzyme inhibitors; *C*=calcium channel blockers; *Cd*=dihydropyridine calcium channel blockers; *Cnd*=non-dihydropyridine calcium channel blockers; *D*=diuretics; and *Dp*=potassium-sparing diuretics.

Endpoints: *AD*=Alzheimer disease; *CI*=cognitive impairment defined as dementia or poor performance on screening and/or repeat cognitive testing; *DEM*=dementia; *MCI*=mild cognitive impairment; and *VaD*=vascular dementia.

Covariates: *A*=age; *ALC*=alcohol intake; *BMI*=body mass index; *BP*=blood pressure; *CHL*=total, high- and low-density lipoprotein cholesterol or hypercholesterolemia; *CSID*=score of Community Screening Instrument for Dementia at baseline; *CVA*=stroke; *CVD*=cardiovascular disease; *DM*=diabetes mellitus; *DPR*=depression; *E4*=number of *APOE* ε4 alleles; *ED*=education; *FHD*=family history of dementia; *HD*=heart disease; *HT*=hypertension; *IS*=living independently as opposed to sheltered care; *MMSE*=score of Mini Mental State Examination at baseline; *PAD*=peripheral artery disease; *R*=race; *S*=sex; *SMK*=smoking; *SF*=sampling frame; *SBP*=systolic blood pressure; and *SIDBP*=systolic and diastolic blood pressure.

Effect size: relative risk associated with antihypertensive drug treatment.

PERSPECTIVES AND CONCLUSIONS

Although hypertension has long been recognized to play a central role in the pathogenesis of VaD, its identification as an equipotent risk factor for AD had to await the final years of the twentieth century. Whether or not blood pressure lowering can prevent AD and to what extent calcium channel blockade provides specific protection against cognitive decline, is an issue with potentially far-reaching implications for public health. Medical treatment of established dementia has only marginal benefit and is not cost-effective [107]. Prevention is the only way to counteract the epidemic of AD in the world's aging populations. Public research bodies, regulators, and the pharmaceutical industry should no longer remain indifferent, but take up the challenge [108-109].

Our review also illustrates that research into dementia requires a comprehensive multidisciplinary approach. Basic researchers, neurologists, geriatricians, and cardiovascular physicians should join forces and start developing a common language transcending the one-sided container approaches of the past decennia. Reviewers and editors should facilitate this process. In scrutinizing submitted research papers, they might adhere to more stringent standards with regard to the diagnostic instruments that have been administered and check whether essential confounders have been sufficiently accounted for. Lack of standardization in the conduct and analysis of studies prevented the computation of pooled statistic from Tables 1 to 4. Finally, publication of cross-sectional and nonrandomized studies, which only provide the lowest level of scientific evidence and which can only be hypothesis generating, should be discouraged in favor of prospective surveys and randomized clinical trials, respectively.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Sandra Covens, Katrien Staessen, and Renilde Wolfs for their expert help in searching the literature and keeping the Reference Manager database updated.

SOURCES OF FUNDING

The authors did not receive any funding for writing the review. The corresponding author had full access to all data and had final responsibility for the decision to submit the manuscript for publication.

CONFLICT OF INTEREST STATEMENT

JA Staessen consulted for pharmaceutical companies and received funding for studies, seminars, and travel from manufacturers of drugs that lower blood pressure. T Richart and WH Birkenhäger have no conflict of interest to declare.

REFERENCES

[1] Vagnucci AH, Jr., Li WW: Alzheimer's disease and angiogenesis. *Lancet.* 2003;361:605–608.

[2] Blennow K, de Leon MJ, Zetterberg H: Alzheimer's disease. *Lancet.* 2006;368:387–403.

[3] Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS): Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. *Lancet.* 2001;357:169–175.

[4] Qiu C, Winblad B, Fastbom J, Fratiglioni L: Combined effects of *APOE* genotype, blood pressure, and antihypertensive drug use on incident AD. *Neurology.* 2003;61:655–660.

[5] Qiu C, Winblad B, Fratiglioni L: The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol.* 2005;4:487–499.

[6] Casserly I, Topol E: Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. *Lancet.* 2004;363:1139–1146.

[7] Román GC, Kalaria RN: Vascular determinants of cholinergic deficits in Alzheimer disease and vascular dementia. *Neurobiol Aging.* 2006 (in press).

[8] Fratiglioni L, De Ronchi d, Agüero-Torres H: Worldwide prevalence and incidence of dementia. *Drugs Aging.* 1999;15:365–375.

[9] Staessen JA, Richart T, Birkenhäger WH. Less atherosclerosis and lower blood pressure for a meaningful life perspective with more brain. *Hypertension* 2007;49:389-400.

[10] Beaglehole R, A Irwin, T Prentice: *The World Health Report 2003 – Shaping the Future.* Geneva, Switzerland, World Health Organization, 2003.

[11] Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M, for Alzheimer's Disease International: Global prevalence of dementia: a Delphi consensus study. *Lancet.* 2005;366:2112–2117.

[12] Brookmeyer R, Gray S, Kawas C: Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health.* 1998;88:1337–1342.

[13] Román GC: Vascular dementia revisited: diagnosis, pathogenesis, treatment, and prevention. *Med Clin North Am.* 2002;86:477–499.

[14] Román GC: Vascular dementia. Advances in nosology, diagnosis, treatment and prevention. *Panminerva Med.* 2004;46:207–215.

[15] Pasquier F, Leys D: Why are stroke patients prone to develop dementia? *J Neurol.* 1997;244:135–142.

[16] Tatemichi TK, Paik M, Bagiella E, Desmond DW, Stern Y, Sano M, Hauser WA, Mayeux R: Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study. *Neurology.* 1994;44:1885–1891.

[17] Loeb C, Gandolfo C, Croce R, Conti M: Dementia associated with lacunar infarction. *Stroke.* 1992;23:1225–1229.

[18] McCormick WC, Abrass IB: Shifting thinking about memory impairment. *Lancet.* 1998;352 (suppl IV):6.

[19] Cohen HJ, Feussner JR, Weinberger M, Carnes M, Hamdy RC, Hsieh F, Phibbs C, Lavori P: A controlled trial of inpatient and outpatient geriatric evaluation and management. *N Engl J Med.* 2002;346:905–912.

[20] Sargolini F, Fyhn M, Hafting T, McNaughton B, Witter MP, Moser EI, Moser MB: Conjunctive representation of position, direction, and velocity in entorhinal cortex. *Science.* 2006;312:758–762.

[21] Agamanolis DP: An Illustrated Interactive Course for Medical Students and Residents. Chapter Nine. Degenerative Diseases (accessed on August 19, 2006).

[22] Maurer K, Volk S, Gerbaldo H: Auguste D and Alzheimer's disease. *Lancet.* 2002;349:1546–1549.

[23] Jicha GA, Parisi JE, Dickson DW, Johnson K, Cha R, Ivnik RJ, Tangalos EG, Boeve BF, Knopman DS, Braak H, Petersen RC: Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Arch Neurol.* 2006;63:674–681.

[24] van der Flier WM, van Straaten ECW, Barkhof F, Verdelho A, Madureira S, Pantoni L, Inzitari D, Erkinjuntti T, Crisby M, Waldemar G, Schmidt R, Fazekas F, Scheltens P, on behalf of the LADIS Group: Small vessel disease and general cognitive function in nondisabled elderly. The LADIS Study. *Stroke.* 2005;36:2116–2120.

[25] Gurol ME, Irizarry MC, Smith EE, Raju S, Diaz-Arrastia R, Bottiglieri T, Rosand J, Growdon JH, Greenberg SM: Plasma □-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy. *Neurology.* 2006;66:23–29.

[26] Schneider JA, Wilson RS, Bienias JL, Evans DA, Bennett DA: Cerebral infarctions and the likelihood of dementia from Alzheimer disease. *Neurology.* 2004;62:1148–1155.

[27] Nagata K, Kondo Y, Atchison R, Sato M, Satoh Y, Watanabe Y, Hirata Y, Yokoyama E: Vascular and metabolic reserve in Alzhiemer's disease. *Neurobiol Aging.* 2000;21:301–307.

[28] Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR: Brain infarction and the clinical expression of Alzheimer's disease. The nun study. *JAMA.* 1997;277:813–817.

[29] Yip AG, McKee AC, Green RC, Wells J, Young H, Cupples LA, Farrer LA: *APOE*, vascular pathology, and the AD brain. *Neurology.* 2005;65:259–265.

[30] Honig LS, Kukull W, Mayeux R: Atherosclerosis and AD. Analysis of data from the US National Alzheimer's Coordinating Center. *Neurology.* 2005;64:494–500.

[31] Lojkowska W, Ryglewicz D, Jedrzejczak T, Minc S, Jakubowska T, Jarosz H, Bochynska A: The effect of cholinesterase inhibitors on the regional blood flow in patients with Alzheimer's disease and vascular dementia. *J Neurol Sci.* 2003;216:119–126.

[32] Ceravolo R, Volterrani D, Tognoni G, Dell'Agnello G, Manca G, Kiferle L, Rossi C, Logi C, Strauss HW, Mariani G, Murri L: Cerebral perfusional effects of cholinesterase inhibitors in Alzheimer disease. *Clin Neuropharmacol.* 2004;27:166–170.

[33] Blin J, Ivanoiu A, Coppens A, De Volder A, Labar D, Michel C, Laterre EC: Cholinergic neurotransmission has different effects on cerebral glucose consumption and blood flow in young normals, aged normals, and Alzheimer's disease patients. *Neuroimage.* 1997;6:335–343.

[34] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA: Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science.* 1993;261:921–923.

[35] Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S: Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet.* 1993;342:697–699.

[36] Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM, for the APOE and Alzheimer Disease Meta Analysis Consortium: Effect of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. *JAMA.* 1997;278:1349–1356.

[37] Cui T, Zhou X, Jin W, Zheng F, Cao X: Gene polymorphism in apolipoprotein E and presenilin-1 in patients with late-onset Alzheimer's disease. *Chin Med J.* 2000;113:340–344.

[38] Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K: Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology.* 2005;64:277–281.

[39] Mancia G, Giannattasio C, Grassi G: Current antihypertensive treatment: can we do better? *Am J Hypertens.* 1999;12:131S–138S.

[40] Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B, Helkala EL, Tuomilehto J, Soininen H, Nissinen A: Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol.* 2005;62:1556–1560.

[41] Waldstein SR, Giggey PP, Thayer JF, Zonderman AB: Nonlinear relations of blood pressure to cognitive function. The Baltimore longitudinal study of aging. *Hypertension.* 2005;45:374–379.

[42] Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, Persson G, Odén A, Svanborg A: 15-year longitudinal study of blood pressure and dementia. *Lancet.* 1996;347:1141–1145.

[43] Kilander L, Nyman H, Boberg M, Hansson L, Lithell H: Hypertension is related to cognitive impairment. A 20-year follow-up of 999 men. *Hypertension.* 1998;31:780–786.

[44] Swan GE, Carmelli D, Larue A: Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. *Stroke.* 1998;29:2334–2340.

[45] Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Jack LM, Carmelli D: Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology.* 1998;51:986–993.

[46] Tzourio C, Dufouil C, Ducimetière P, Alpérovitch A, for the EVA Study Group: Cognitive decline in individuals with high blood pressure. A longitudinal study in the elderly. *Neurology.* 1999;53:1948–1952.

[47] Elkins JS, Yaffe K, Cauley JA, Fink HA, Hillier TA, Johnson SC: Pre-existing hypertension and the impact of stroke on cognitive function. *Ann Neurol.* 2005;58:68–74.

[48] Peila R, White LR, Petrovich H, Masaki K, Ross GW, Havlik RJ, Launer LJ: Joint effect of the *APOE* gene and midlife systolic blood pressure on late-life cognitive impairment. The Honolulu-Asia aging study. *Stroke.* 2001;32:2882–2889.

[49] Strassburger TL, Lee HC, Daly EM, Szczepanik J, Krasuski JS, Mentis MJ, Salerno JA, DeCarli C, Schapiro MB, Alexander GE: Interactive effects of age and hypertension on volumes of brain structures. *Stroke.* 1997;28:1410–1417.

[50] Seux ML, Thijs L, Forette F, Staessen JA, Birkenhäger WH, Bulpitt CJ, Girerd X, Jääskivi M, Vanhanen H, Kivinen P, Yodfat Y, Vänskä O, Antikainen R, Laks T, Webster JR, Hakamäki T, Lehtomäki E, Lilov E, Grigirov M, Janculova K, Halonen K, Kohonen-Jalonen P, Kermowa R, Nachev C, Tuomilehto J: Correlates of cognitive status of old patients with isolated systolic hypertension: the Syst-Eur Vascular Dementia Project. *J Hypertens.* 1998;16:963–969.

[51] Elias PK, Elias MF, Robbins MA, Budge MM: Blood pressure-related cognitive decline: does age make a difference? *Hypertension.* 2004;44:625–630.

[52] Kilander L, Nyman H, Boberg M, Lithell H: The association between low diastolic blood pressure in middle age and cognitive function in old age. A population-based study. *Age Ageing.* 2000;29:243–248.

[53] Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR: Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology.* 2001;56:42–48.

[54] Alves de Moraes S, Szklo M, Knopman D, Sato R: The relationship between temporal changes in blood pressure and changes in cognitive function: Atherosclerosis Risk In Communities (ARIC) Studies. *Prev Med.* 2002;35:258–263.

[55] Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB: Lower cognitive function in the presence of obesity and hypertension: the Framingham Heart Study. *Int J Obes.* 2003;27:260–268.

[56] André-Petersson L, Elmståhl S, Hagberg B, Janzon L, Reinprecht F, Steen G: Is blood pressure at 68 an independent predictor of cognitive decline at 81? Results from follow-up study 'Men born in 1914', Malmö, Sweden. *Aging Ment Health.* 2003;7:61–72.

[57] Shah RC, Wilson RS, Bienias JL, Arvanitakis Z, Evans DA, Bennett DA: Relation of blood pressure to risk of incident Alzheimer's disease and change in global cognitive function in older persons. *Neuroepidemiology.* 2006;26:30–36.

[58] Bohannon AD, Fillenbaum GG, Pieper CF, Hanlon JT, Blazer DG: Relationship of race/ethnicity and blood pressure to change in cognitive function. *J Am Geriatr Soc.* 2002;50:424–429.

[59] Insel KC, Palmer RF, Stroup-Benham CA, Markides KS, Espino DV: Association between change in systolic blood pressure and cognitive decline among elderly Mexican American: data from the hispanic established population for epidemiology study of the elderly. *Exp Aging Res.* 2005;31:35–54.

[60] Hebert LE, Scherr PA, Bennett DA, Bienias JL, Wilson RS, Morris MC, Evans DA: Blood pressure and late-life cognitive function change. A biracial longitudinal population study. *Neurology.* 2004;62:2021–2024.

[61] Kuo HK, Jones RN, Milberg WP, Tennstedt S, Talbot L, Morris JN, Lipsitz LA: Effect of blood pressure and diabetes mellitus on cognitive and physical functions in older adults: a longitudinal analysis of the advanced cognitive training for independent and vital elderly cohort. *J Am Geriatr Soc.* 2005;53:1154–1161.

[62] Hassing LB, Hofer SM, Nilsson SE, Berg S, Pedersen NL, McClearn G, Johansson B: Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study. *Age Ageing.* 2004;33:355–361.

[63] Yamada M, Kasagi F, Sasaki H, Masunari N, Mimori Y, Suzuki G: Assocociation between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study. *J Am Geriatr Soc.* 2003;51:410–414.

[64] Kivipelto M, Helkala EL, Hänninen T, Laakso MP, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A: Midlife vascular risk factors and late-life mild cognitive impairment. A population-based study. *Neurology.* 2001;56:1683–1689.

[65] Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissien A: Midlife vacsular risk factors and Alzheimer's disease in later life: longitudinal population based study. *Br Med J.* 2001;322:1447–1451.

[66] Launer LJ, Webster Ross G, Petrovitch H, Masaki K, Foley D, White LR, Havlik RJ: Midlife blood pressure and dementia: the Honolulu-Asia Aging Study. *Neurobiol Aging.* 2000;21:49–55.

[67] Ruitenberg A, Skoog I, Ott A, Aevarsson O, Witteman JCM, Lernfelt B, van Harskamp F, Hofman A, Breteler MMB: Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 study. *Dement Geriatr Cogn Disord.* 2001;12:33–39.

[68] Solfrizzi V, Panza F, Colacicco AM, D'Introno A, Capurso C, Torres F, Grigoletto F, Maggi S, Del Parigi A, Reiman EM, Caselli RJ, Scafato E, Farchi G, Capurso A, for the Italian Longitudinal study on Aging Working group: Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology.* 2004;63:1882–1891.

[69] Borenstein AR, Wu Y, Mortimer JA, Schellenberg GD, McCormick WC, Bowen JD, McCurry S, Larson EB: Developmental and vascular risk factors for Alzheimer's disease. *Neurobiol Aging.* 2005;26:325–334.

[70] Posner HB, Tang MX, Luchsinger J, Lantigua R, Stern Y, Mayeux R: The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. *Neurology.* 2002;58:1175–1181.

[71] Kuller LW, Lopez OL, Newman A, Beauchamps NJ, Burke G, Dulberg C, Fitzpatrick A, Fried L, Haan MN: Risk factors for dementia in the Cardiovascular Health Cognition Study. *Neuroepidemiology.* 2003;22:13–22.

[72] Petrovitch H, White LR, Izmirilian G, Ross GW, Havlik RJ, Markesbery W, Nelson J, Davis DG, Hardman J, Foley DJ, Launer LJ: Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. *Neurobiol Aging.* 2000;21:57–62.

[73] de Leeuw FE, de Groot JC, Oudkerk M, Witteman JCM, Hofman A, van Gijn J, Breteler MMB: Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain.* 2002;125:765–772.

[74] den Heijer T, Skoog I, Oudkerk M, de Leeuw FE, de Groot JC, Hofman A, Breteler MMB: Association between blood pressure levels over time and brain atrophy in the elderly. *Neurobiol Aging.* 2003;24:307–313.

[75] Goldstein IB, Bartzokis G, Guthrie D, Shapiro D: Ambulatory blood pressure and the brain. A 5-year follow-up study. *Neurology.* 2005;64:1846–1852.

[76] Zhang H, Thijs L, Kuznetsova T, Fagard RH, Li X, Staessen JA: Progression of hypertension in the non-hypertensive participants in the Flemish Study on Environment, Genes and ealth Outcomes. *J Hypertens.* 2006;24:1719–1727.

[77] Petitti DB, Crooks VC, Buckwalter JG, Chiu V: Blood pressure levels before dementia. *Arch Neurol.* 2005;62:112–116.

[78] Hanon O, Latour F, Seux ML, Lenoir H, Forette F, Rigaud AS, the REAL.FR group: Evolution of blood pressure in patients with Alzheimer's disease: a one year survey of a French cohort (REAL.FR). *J Nutr Health Aging.* 2005;9:106–111.

[79] Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K: Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension.* 2001;38:852–857.

[80] Guo Z, Fratiglioni L, Zhu L, Fastbom J, Winblad B, Viitanen M: Occurrence and progression of dementia in a community population aged 75 years and older. Relationship with medication use. *Arch Neurol.* 1999;56:991–996.

[81] in't Veld BA, Ruitenberg A, Hofman A, Stricker BHC, Breteler MMB: Antihypertensive drugs and incidence of dementia: the Rotterdam Study. *Neurobiol Aging.* 2001;22:407–412.

[82] Morris MC, Scherr PA, Hebert LE, Glynn RJ, Bennett DA, Evans DA: Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. *Arch Neurol.* 2001;58:1640–1646.

[83] Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, McDowell I: Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol.* 2002;156:445–453.

[84] Murray MD, Lane KA, Gao S, Evans RM, Unverzagt FW, Hall KS, Hendrie H: Preservation of cognitive function with antihypertensive medications. A longitudinal analysis of a community-based sample of African Americans. *Arch Intern Med.* 2002;162:2090–2096.

[85] Yasar S, Corrada M, Brookmeyer R, Kawas C: Calcium channel blockers and risk of AD: the Baltimore Longitudinal Study of Aging. *Neurobiol Aging.* 2005;26:157–163.

[86] Hajjar I, Catoe H, Sixta S, Boland R, Johnson D, Hirth V, Wieland D, Eleazer P: Cross-sectional and longitudinal association between antihypertensive medications and cognitive impairment in an elderly population. *J Gerontol.* 2005;60A:67–73.

[87] Khachaturian AS, Zandi PP, Lyketsos CG, Hayden KM, Skoog I, Norton MC, Tschanz JT, Mayer LS, Welsh-Bohmer KA, Breitner J: Antihypertensive medication use and incident Alzheimer disease: the Cache County Study. *Arch Neurol.* 2006;63:686–692.

[88] Tervo S, Kivipelto M, Hänninen T, Vanhanen M, Hallikainen M, Mannermaa A, Soininen H: Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. *Dement Geriatr Cogn Disord.* 2004;17:196–203.

[89] Heckbert SR, Longstreth WT, Jr., Psaty BM, Murros KE, Smith NL, Newman AB, Williamson JD, Bernick C, Furberg CD: The association of antihypertensive agents with MRI white matter findings and the Modified Mini-Mental State Examination in older adults. *J Am Geriatr Soc.* 1997;45:1423–1433.

[90] Maxwell CJ, Hogan DB, Ebly EM: Calcium-channel blockers and cognitive function in elderly people: results from the Canadian Study of Health and Aging. *Can Med Ass J.* 1999;161:501–506.

[91] Staessen JA, Li Y, Thijs L, Wang JG: Blood pressure reduction and cardiovascular prevention: an update including the 2003-2004 secondary prevention trials. *Hypertens Res.* 2005;28:385–407.

[92] Hansson L, Hedner T, Dahlöf B: Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. *Blood Press.* 1992;1:113–119.

[93] Prince MJ, Bird AS, Blizard RA, Mann AH: Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's treatment trial of hypertension in older adults. *Br Med J.* 1996;312:801–805.

[94] Cervilla JA, Prince M, Joels S, Lovestone S, Mann A: Long-term prediction of cognitive outcome in a cohort of older people with hypertension. *Brit J Psychiatry.* 2000;177:66–71.

[95] Fogari R, Mugellini A, Zoppi A, Marasi G, Pasotti C, Poletti L, Rinaldi A, Preti P: Effects of valsartan compared with enalapril on blood pressure and cognitive function in elderly patients with essential hypertension. *Eur J Clin Pharmacol.* 2004;59:863–868.

[96] Tedesco MA, Ratti G, Mennella S, Manzo G, Grieco M, Rainone AC, Iarussi D, Iacono A: Comparison of losartan and hydrochlorothiazide on cognitive function and quality of life in hypertensive patients. *Am J Hypertens.* 1999;12:1130–1134.

[97] SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA.* 1991;265:3255–3264.

[98] Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, Bossini A, Fagard R, Gil-Extremera B, Laks T, Kobalava Z, Sarti C, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Birkenhäger WH, for the Syst-Eur Investigators: The prevention of dementia with antihypertensive treatment. New evidence from the Systolic Hypertension in Europe (Syst-Eur) Study [erratum published in The Archives of Internal Medicine 2003, volume 163, January 27, p 241]. *Arch Intern Med.* 2002;162:2046–2052.

[99] The PROGRESS Collaborative Group: Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med.* 2003;163:1069–1075.

[100] Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A, for the SCOPE Study Group: The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomised double-blind intervention trial. *J Hypertens.* 2003;21:875–886.

[101] Di Bari M, Pahor M, Franse LV, Shorr RI, Ferrucci L, Somes GW, Applegate WB: Dementia and disability outcomes in large hypertension trials: lessons learned from the Systolic Hypertension in the Elderly Program (SHEP) trial. *Am J Epidemiol.* 2001;153:72–78.

[102] Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhäger WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators: Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension [erratum published in The Lancet 1997, volume 350, November 29, p 1636]. *Lancet.* 1997;350:757–764.

[103] Forette F, Seux ML, Staessen JA, Thijs L, Birkenhäger WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster B, Yodfat Y, Fagard R, on behalf of the Syst-Eur Investigators: Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet.* 1998;352:1347–1351.

[104] Skoog I, Lithell H, Hansson L, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A, for the SCOPE Study Group: Effect of baseline cognitive function and antihypertensive treatment on cognitive function: Study on COgnition and Prognosis in the Elderly (SCOPE). *Am J Hypertens.* 2005;18:1052–1059.

[105] Wang JG, Staessen JA, Birkenhäger WH: Antihypertensive treatment and prevention of stroke and dementia. *Sem Cerebrovasc Dis Stroke.* 2003;3:155–164.

[106] Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J, PROGRESS Collaborative Group: Effect of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med.* 2003;163:1069–1075.

[107] AD2000 Collaborative Group: Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet.* 2004;363:2105-2115.

[108] Staessen JA, Birkenhäger WH: Cognitive impairment and blood pressure. Quo usque tandem abutere patientia nostra? *Hypertension.* 2004;44:612-613.

[109] Birkenhäger WH, Staessen JA. Progress in cardiovascular diseases. Cognitive function in essential hypertension. *Progress in Cardiovascular Diseases* 2006;49:1-10.

[110] Luchsinger JA, Reitz C, Honig LS, Tang M-X, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology* 2005;65:545-551.