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Less Atherosclerosis and Lower Blood Pressure for a Meaningful Life Perspective With More Brain

Jan A. Staessen, Tom Richart, Willem H. Birkenhäger

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.^{1,2} 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.³ 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.

Epidemiology of Dementia

Across 36 cross-sectional studies, the prevalence of dementia increased exponentially from 0.3% to 1.0% in subjects aged 60 to 64 years to 10% to 20% in octogenarians and to >40% in the ninth decade of life.³ In 15 longitudinal studies, the incidence of dementia showed a similar age-related dependency with rates expressed in new cases per 1000 person-years ranging from 0.4 to 4 at 60 to 64 years to 20 to >40 at 80 to 85 years.³ Currently, 24.3 million people have dementia with an annual worldwide incidence of 4.6 million new cases.⁴ Because of the aging of populations, the number of demented patients will increase 2-fold every 20 years to 81.1 million by 2040, with >60% living in developing countries.⁴ The 2003 World Health Report⁵ estimated that adults aged ≥ 60 years lost ≈ 8.6 million disability-adjusted life years because of AD or other dementias. 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.⁵ In the United States, the number of demented patients with roughly triple, from 4.6 million in 1998 to 16 million by 2050.⁶

Pathogenesis of Dementias

VaD

Poststroke dementia is the most common form of VaD. In a case-control study nested within the Framingham cohort, the relative risk of dementia in stroke survivors compared with controls varied from 2.0 to 2.8, depending on the covariates considered for adjustment.⁷ Of the incident dementia cases, 51% were diagnosed as having VaD or mixed dementia, whereas this proportion was only 4% among the control subjects without a history of stroke.⁷

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).^{8,9} Of particular importance in older patients is subcortical small vessel disease of the medullary arteries, which perpendicularly penetrate the brain cortex into the subjacent white substance without intertwining branches other than very fine capillaries, thus constituting many independent small vascular territories. Exposure of these small brain vessels to highly pulsatile pressure and flow explains microvascular damage,¹⁰ resulting in white matter damage, lacunas, and loss of cortical connections.⁸ Multiple infarction dementia exhibits a stepwise but unpredictable course, depending on the size, localization, and number of ischemic insults.⁹ Subcortical VaD has a more insidious character without sensory-motor manifestations but with progressive changes in personality, mood, behavior, or cognition (Figure 1).

AD

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.^{1,2} Interaction between these brain structures plays a crucial role in memory consolidation, memory optimization during sleep, and spatial orientation. The prevailing viewpoint on the pathogenesis of AD rests on the extraneuronal and intraneuronal accumulation of misfolded protein, amy-

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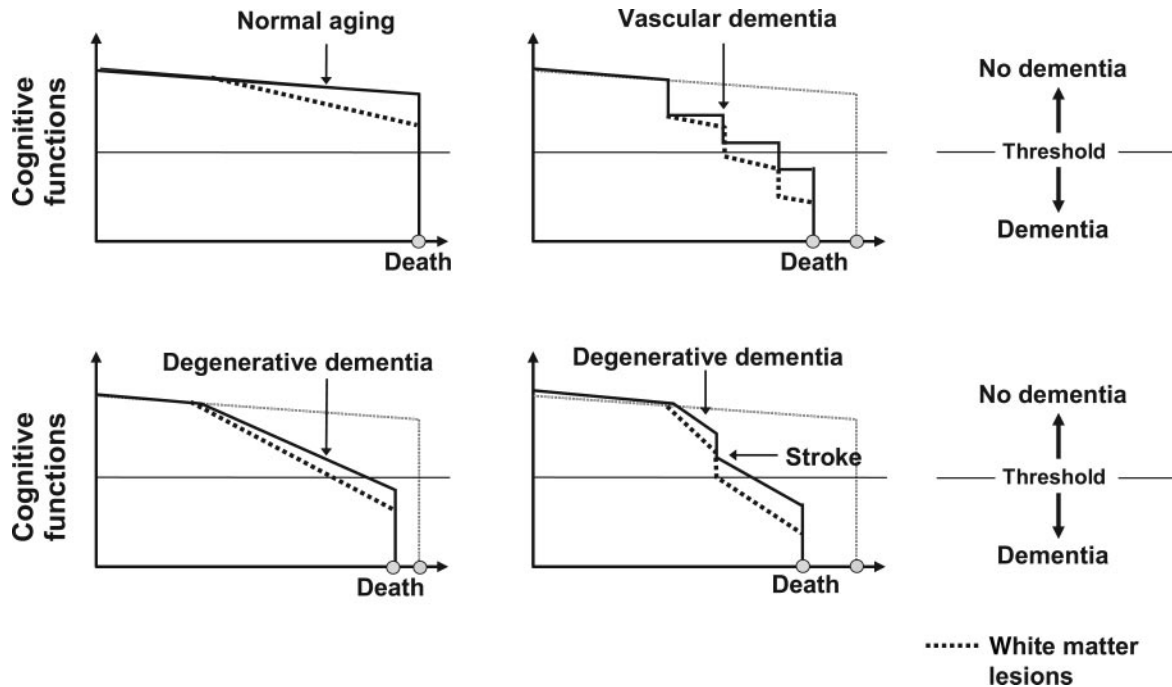


Figure 1. Time course of cognitive functions (reproduced with permission from Reference 9).

loid β -peptide ($A\beta$), which starts a pathogenetic cascade resulting in neurotoxicity.² $A\beta$ has selective toxicity for the hippocampus and entorhinal cortex, while sparing the cerebellum. Deposits of $A\beta$ form senile plaques. Neurofibrillary tangles are the second histopathologic hallmark of AD.² They consist of hyperphosphorylated microtubule-associated protein τ . They aggregate as pairs of filaments that twist around one another: so-called paired helical filaments. These filamentous inclusions displace organelles, destabilize the cytoskeleton, and impair axoplasmic flow, thereby affecting nutrition of axon terminals and dendrites.

Mild cognitive impairment indicates a syndrome defined as a cognitive decline greater than expected for an individual's age and education. In adults >65 years of age, it has a prevalence ranging from 3% to 19%.¹¹ Many patients with mild cognitive impairment have minor histopathologic AD changes, and more than half progress to full blown AD.^{11,12}

Neurodegeneration and Atherosclerosis

Accumulating evidence suggests a strong link among AD, cardiovascular risk factors, and atherosclerosis. In multivariate-adjusted longitudinal studies, the incidence of dementia independently increased with pre-existing cardiovascular disease, the metabolic syndrome, skinfold thickness, body mass index, hypercholesterolemia, diabetes mellitus, hyperhomocysteinemia, smoking, and/or high-sensitivity C-reactive protein, whereas higher education, more exercise at middle age, and moderate alcohol consumption were protective.^{1,13}

Neuroimaging¹⁴ and postmortem histopathologic¹⁵ 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. 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.⁹ Moreover, recent 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). Indeed, cholinergic agents stimulate regional cerebral blood flow in patients with AD or VaD.¹⁶

Experimental studies likewise support the convergence between $A\beta$ and vascular factors in the pathogenesis of dementia. $A\beta$ constricts human cerebral arteries.¹⁷ $A\beta$ attenuates endothelium-mediated dilatation in cerebral arteries by production of reactive oxygen radicals and impairs the increase in neocortical blood flow in response to somatosensory activation.¹⁸ Furthermore, transgenic mice overexpressing mutated forms of amyloid precursor protein, from which misfolded $A\beta$ originates, show a reduction in resting¹⁷ and stimulated¹⁸ cerebral blood flow and an impaired autoregulation of the cerebral circulation.¹⁹ Human platelets contain membrane-associated amyloid precursor protein.²⁰ Macrophages in human carotid plaque, which phagocytize platelets after intraplaque microhemorrhages, can process amyloid precursor protein into $A\beta$.²⁰

Other studies suggest the involvement of cholesterol metabolism in the pathogenesis of AD. In cell cultures, increased²¹ and decreased²² cholesterol concentrations stimulate or repress the generation of $A\beta$ from amyloid precursor protein, respectively. The apolipoprotein E $\epsilon 4$ 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.²³ The $\epsilon 4$ allele enhances the risk 3-fold in heterozygotes and by a factor 15 in homozygotes.²³ Each allele copy lowers the age of onset by ≈ 10 years.²⁴ Apolipoprotein E acts as a cholesterol transporter in the brain, with the $\epsilon 4$ variant being less efficient in the reuse of membrane lipids and neuronal

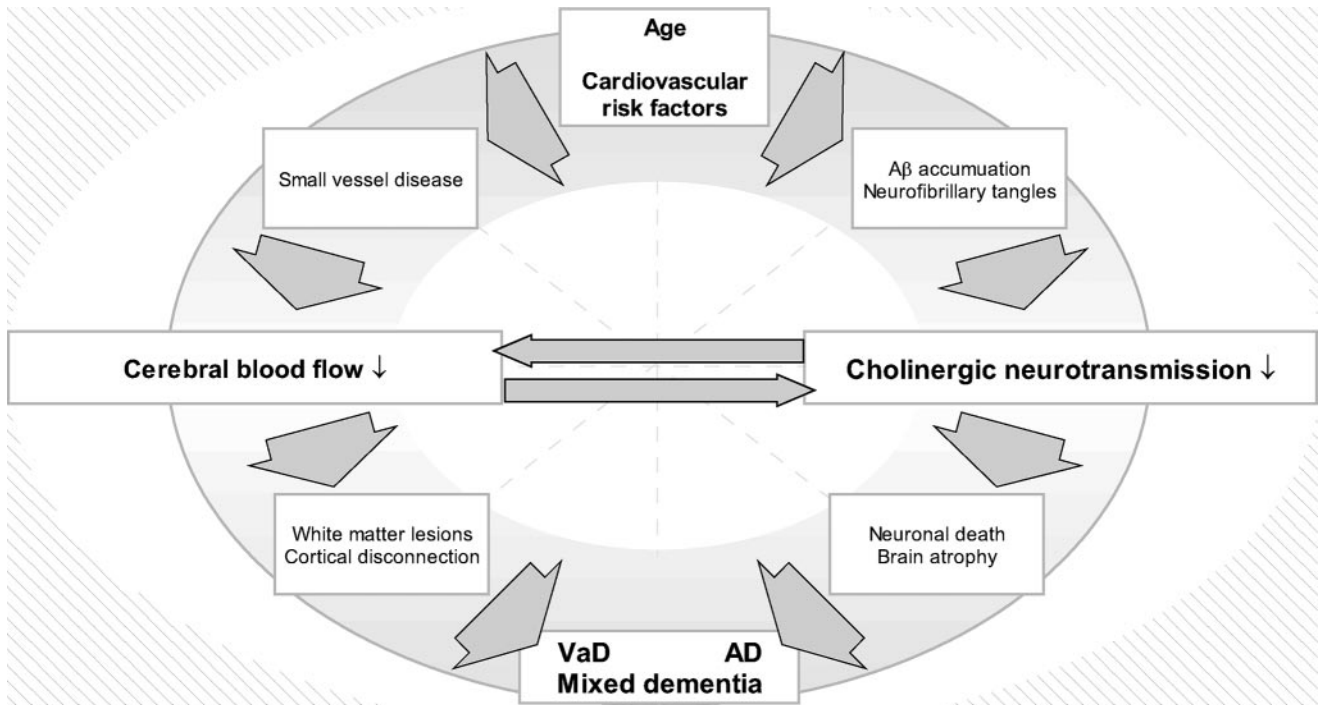


Figure 2. Overlap between neurodegenerative and VaD and interaction between cholinergic factors and cerebral blood flow.

repair.²⁵ The $\epsilon 3$ and $\epsilon 4$ variants play a critical and isoform-specific role in plaque formation.²⁶ The apolipoprotein E $\epsilon 4$ allele accounts for most of the genetic risk in AD.^{1,2}

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 of >90% to become hypertensive during the remainder of his lifetime.²⁷ Studies on the association between cognition and blood pressure can be subdivided into those with a cross-sectional versus longitudinal design. The end point in these studies can be disease outcomes, such as dementia, AD, or VaD; morphological or functional alterations of the brain, as documented by histopathologic autopsy studies or modern neuroimaging techniques; or 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, or composite scores of specific tests.

Cross-Sectional Studies

Cross-sectional studies, reviewed elsewhere,²⁸ observed positive and independent associations of blood pressure, analyzed as a continuous or dichotomized variable, with cognitive impairment as assessed by the Mini Mental State Examination or multiple cognitive tests. By contrast, other cross-sectional studies did not find any association or noticed a U-shaped relation.

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. Histological lesions, such as neurofibrillary tangles or an accelerated rate of neuronal atrophy in the medial temporal lobe of the brain, for decades, may precede overt dementia. Two Framingham reports^{29,30} dramatically illustrated the shortfall of the cross-sectional approach. In stroke-free Framingham participants, there was no relation between the scores of 8 cognitive tests, administered in 1976–1978, and the concurrently measured blood pressure, irrespective of whether the analysis included or excluded patients on antihypertensive drug treatment.²⁹ However, higher blood pressure levels over 5 earlier biennial examinations (1956–1964), when few hypertensive patients were taking antihypertensive medications, significantly predicted lower scores of attention, memory, and global cognition in 1976–1978.³⁰ This inverse temporal association was consistent for systolic and diastolic blood pressure and withstood adjustment for sex, age, cigarette smoking, alcohol consumption, education, and occupation.³⁰

Longitudinal Cohort Studies

In 1996, Skoog et al³¹ published one of the first longitudinal studies on the incidence of dementia in relation to blood pressure. They recruited 382 nondemented 70-year-old residents of Göteborg, Sweden (57.8% women), of whom 302, 205, and 94 were available for reassessment at 75, 79, and 85 years, respectively. Participants who developed dementia at age 79 to 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).³¹ Patients specifically developing AD or VaD had higher diastolic blood pressure at ages 70 and 75, respectively.³¹

Although based on relatively few subjects, the seminal report by Skoog et al³¹ set the stage for subsequent studies published in the second half of the 1990s.^{32–35} These multivariate-adjusted analyses confirmed that at a relatively high diastolic blood pressure (≥ 75 mm Hg versus ≤ 70 mm Hg) at age 50,³² a persistently elevated systolic blood pressure (≥ 140 mm Hg) at ages ranging from 43³⁴ to 75³³ years, or stage 2 hypertension (≥ 160 mm Hg systolic and ≥ 95 mm Hg diastolic) within the 59 to 71 age bracket³⁵ consistently predicted worse cognitive performance^{32–35} or more severe white-matter lesions³⁴ at ages ranging from 63³⁵ to 79³⁴ years. To further clarify the role of blood pressure in the pathogenesis of cognitive impairment, we performed a systematic review of the prospective studies published since 2000 until early 2006, 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)^{36–47}; the incidence of cognitive dysfunction, dementia, AD, or VaD (Table 2)^{42,48–61}; or the appearance of brain lesions in histopathologic or neuroimaging studies (Table 3).^{62–65} For each of these 3 end points, we ordered the reports according to the age at enrollment.

All of the studies of cognitive function, involving subjects on average < 70 years old at enrollment (Table 1),^{36–41} uniformly showed a significantly lower performance or a more rapid decline of cognitive function with higher blood pressure, although in 1 cohort only for stage 3 hypertension.⁴¹ At more advanced age,^{42–47} point estimates went in the same direction but only reached significance in the normotensive Hispanic Established Populations for Epidemiologic Studies of the Elderly cohort⁴⁴ and in the Active Cognitive Training for Independent and Vital Elderly Trial.⁴⁶

Among the studies with cognitive impairment as a categorical end point (Table 2),^{42,48–61} those using a dichotomized test score^{53,57} classified from 15%⁵³ to 50%⁵⁷ of the participants as cognitively impaired and reported positive associations with hypertension. Two studies^{50,56} found no association of mild cognitive impairment with hypertension earlier in life. Studies with dementia,^{48,52,54} AD,^{42,49,51,52,54,55,58–61} or VaD^{49,54,59} as the end point demonstrated a significantly positive association with ≥ 1 blood pressure index, if follow-up started from middle age rather than old age.^{48,51,52,54} Remarkably, 1 study found an inverse association of AD with blood pressure in subjects recruited at the upper end of the age spectrum (mean age 87 years).⁵⁵ 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.⁶⁶ 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 because of a learning effect.⁶⁶ 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.⁶⁶

In summary, our overview shows that hypertension, especially when already present at 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 50⁶⁷ or because systolic blood pressure falls in the very old.³¹ Finally, 1 autopsy report⁶² and 3 brain imaging studies^{63–65} with longitudinal perspective observed independent and positive associations between brain lesions and blood pressure indexes (Table 3).^{62–65}

Low Blood Pressure as Manifestation of Dementia

Already in 1996, Skoog et al³¹ noticed that with advancing age all of the subjects in his study experienced a decrease in blood pressure but that the fall in systolic and diastolic blood pressure was larger in patients who developed dementia than in their nondemented counterparts. A retrospective review of the medical charts of 1133 women (≥ 75 years) covering 10 years⁶⁸ 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 of the groups.⁶⁸ In a cohort of 242 French patients with moderate AD (mean age: 78 years; 74% women)⁶⁹ blood pressure significantly fell over 1 year of follow-up, independent of sex, age, body mass index, and antihypertensive drug treatment.

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 after 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.⁷⁰

Reversibility of Risk Associated With Hypertension

Nonrandomized Observational Studies

Ten prospective studies (Table 4)^{35,71–79} 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 end point, the wide range of age at baseline and duration of follow-up, varying sampling frames, and adjustment for different sets of covariates or effect modifiers, such as the apolipoprotein E $\epsilon 4$ polymorphism,^{35,79} made the computation of a pooled association size impossible. Nevertheless, of the 10 studies (Table 4),^{35,71–79} 8 reported that antihypertensive drug treatment lowered the risk of cognitive decline, the reduction being significant in 5 reports,^{71,72,75,77,78} and proportional to duration of treatment.⁸⁰ 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

TABLE 1. Association Between Cognitive Function and Blood Pressure Indexes

Study	Outcome	N	FU, y	Age, y	F, %	CVA,%	BP, mm Hg	Covariates	Effect Size (95% CI)	P
MLSH, 2004 ³⁶	ΔV/FC	285	≈9.3	≈35	52	0	134/86 (56)	S, A, BMI, [SP] −0.05 (−0.11 to 0.01) ≈0.13		
								SMK, ALC, [DP] −0.09 (−0.19 to −0.00) ≈0.04		
								OCC, ED, [HT] −0.16 (−0.28 to −0.03) ≈0.01		
Uppsala, 2000 ³⁷	DS VF	463	20	50	0	0	≈131/83 (...)	A, DM, ED, [DP] ≈−1.00 (−1.90 to −0.10) 0.03		
								OCC [DP] ≈−0.32 (−0.65 to −0.03) 0.03		
ARIC, 2001 ³⁸	ΔDSS	10 767	6.0	57	≈66/... (32)	C, R, A, ED, [HT] −0.40 (... to ...) <0.05		
ARIC, 2002 ³⁹	ΔDSS	4 928	6.0	≈57	≈52	0	120/72 (...)	R, A, DM, ED [UHT] −0.90 (... to ...) <0.05		
MLSH, 2004 ³⁶	ΔV/FC	244	≈9.3	58	51	0	152/91 (74)	S, A, BMI, [SP] −0.09 (−0.14 to −0.03) ≈0.002		
								SMK, ALC, [DP] −0.15 (−0.25 to −0.05) ≈0.002		
								OCC, ED, [HT] −0.24 (−0.39 to −0.08) ≈0.002		
Framingham, 2003 ⁴⁰	ΔSCCS	872	≈5.0	67	100	0	132/80 (...)	A, BMI, CHL, [HT] −0.01 (−0.11 to 0.09) 0.88		
								SMK, ALC, [HT] −0.16 (−0.30 to −0.02) 0.04		
Malmö, 2003 ⁴¹	ΔSCCS	128	12.5	68	0	0	≈151/91 (16.7)	AHT, HD, [HT2] 0.31 (0.11 to 0.51) ≈0.001		
								PAD, DM, [HT3] −0.31 (−0.54 to −0.07) ≈0.01		
Clergy members, 2006 ⁴²	ΔSCCS	824	6.5	70	69	...	134/75 (52.0)	S, A, ED [SP] −0.01 (−0.03 to 0.01) 0.34		
								[DP] 0.00 (... to ...) 0.76		
Duke EPESE, 2002 ⁴³	ΔSPMS	3 202	3.0	73	67	6.6	143/79 (52)	R, S, A, [HT] 0.03 (−0.10 to 0.16) 0.68		
Hispanic EPESE, 2005 ⁴⁴	ΔMMSE	1138 (NT)	≈7.0	73	...	4.0	124/75 (0)	S, A, BMI, [SP] 0.80 (−0.38 to 1.98) ≈0.18		
								ΔBMI, CVA, [ΔSP] −0.08 (−0.14 to −0.02) ≈0.008		
								CVD, DM, [SP] −0.10 (−0.49 to 0.29) ≈0.62		
Chicago, 2004 ⁴⁵	ΔSCCS	4 284	5.3	74	62	16.0	140/77 (...)	R, S, A, BPB, [ΔSP] −0.00 (−0.00 to 0.00) 0.30		
								ED, FU [ΔDP] −0.00 (−0.00 to 0.00) 0.70		
ACTIVE, 2005 ⁴⁶	ΔCSR	2 017	1.0	74	76	7.0	.../... (≈41)	R, S, A, BMI, [SH1] −0.18 (−0.34 to −0.02) 0.03		
								CHL, CVA, [SH2] −0.28 (−0.48 to −0.09) 0.005		
OCTO, 2004 ⁴⁷	ΔMMSE	258	≈6.0	≈83	≈70	10.4	160/83 (44)	S, A, SMK, [HT] −0.54 (−1.13 to 0.05) ≈0.07		
								HD, CVA, ED, CTB		

Abbreviations: N indicates No. 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 unreported information that could not be estimated. Studies were ordered according to age at enrolment.

Acronyms: ACTIVE indicates 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; OCTO, origins of variance in the Old-Old.

End points: ΔCSR indicates 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) vs 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; ΔV/FC, annual change in the visualization/fluid composite score as derived from the Wechsler Adult Intelligence Test; VF, verbal fluency test score.

Covariates: A indicates 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; SMK, smoking.

Blood pressure indexes at baseline: DP/SP indicates 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; 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.

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

Study	Outcome	N	Events (Rate per 100)	FU, y	Age, y	F, %	CVA, %	BP, mm Hg	Covariates	Relative Risk (95% CI)	P
KPNC, 2005 ⁴⁸	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 ⁴⁹	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 ⁵⁰	MCI	1409	82 (5.8)	20.9	50	62	...	144/89 (...)	A, BMI	[SH1] 0.8 (0.4 to 1.3) [SH2] 1.2 (0.7 to 2.2) [DH1] 0.9 (0.5 to 1.7)	≈0.36 ≈0.55 ≈0.74
										[DH2] 1.1 (0.7 to 1.9)	≈0.73
North Karelia, 2001 ⁵¹	AD	1409	48 (3.4)	20.9	50	62	...	144/89 (...)	A, BMI, SMK, ALC, CVA, HD, ED	[SH1] 2.1 (0.8 to 5.0) [SH2] 2.8 (0.1 to 7.2) [DH1] 1.4 (0.6 to 3.5) [DH2] 1.7 (0.8 to 3.6)	≈0.09 ≈0.03 ≈0.46 ≈0.16
CAIDE, 2005 ⁵²	DEM	1409	... (5.8)	21.0	50	62	7.2	144/89 (...)	S, A, BMI, CHL, ED, FU	[SH] 1.97 (1.03 to 3.77)	≈0.04
	AD		... (3.8)							[SH] 1.57 (0.78 to 3.14)	≈0.19
HAAS, 2001 ⁵³	CASI	3605	539 (15.0)	26.0	52	0	6.2	132/82 (...)	A, BMI, SMK, ALC, ED	[SH2-E4] 1.8 (1.2 to 2.9) [SH2+E4] 2.9 (1.4 to 6.3)	≈0.01 ≈0.006
HAAS, 2000 ⁵⁴	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) [SH2-T] 3.88 (1.50 to 10.0) [DH1-T] 3.78 (1.59 to 8.95) [DH2-T] 4.00 (1.56 to 10.2)	≈0.65 ≈0.004 ≈0.002 ≈0.003
	AD	3703	118 (3.2)							[SH1-T] 1.23 (0.63 to 2.43) [SH2-T] 1.22 (0.37 to 4.04) [SH2-T] 1.22 (0.37 to 4.04) [DH1-T] 3.49 (1.28 to 9.52) [DH2-T] 4.47 (1.53 to 13.1)	≈0.54 ≈0.74 ≈0.74 ≈0.01 ≈0.005
	Vad	3703	79 (2.1)							[SH1-T] 0.81 (0.21 to 3.19) [SH2-T] 11.8 (3.52 to 39.5) [DH1-T] 3.45 (0.79 to 15.0) [DH2-T] 2.49 (0.46 to 13.4)	≈0.76 <0.001 ≈0.09 ≈0.28
Rotterdam and Gothenburg, 2001 ⁵⁵	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) [DP] 0.95 (0.81 to 1.15)	≈0.67 ≈0.68
Clergy members, 2006 ⁴²	AD	824	151 (18.3)	6.5	70	69	...	134/75 (52.0)	S, A, ED	[SP] 0.95 (0.82 to 1.04) [DP] 1.00 (0.93 to 1.08)	0.25 0.98
ILSA, 2004 ⁵⁶	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
SOF, 2005 ⁵⁷	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 ⁵⁸	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 ⁵⁷	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 ⁵⁹	AD	1259	157 (12.5)	7.0	76	69	12.5	.../... (≈58.0)	R, S, A, HD	[HT] 0.8 (0.6 to 1.1)	≈0.16
	VaD		56 (4.4)							[HT] 1.6 (0.9 to 2.9)	≈0.11
Luchsinger, 2005 ⁶⁰	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 ⁶¹	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 ⁵⁵	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

(Continued)

TABLE 2. (Continued)

Study	Outcome	N	Events (Rate per 100)	FU, y	Age, y	F, %	CVA, %	BP, mm Hg	Covariates	Relative Risk (95% CI)	P
Rotterdam and Gothenburg, 2001 ⁵⁵	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 indicates No. 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 CI. “...” represents unavailable information that could not be estimated. Studies were ordered according to age at enrolment.

Acronyms: CAIDE indicates 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; SOF, Study of Osteoporotic Fractures.

End points: CASI indicates Cognitive Abilities Screening Instrument score below 15th percentile; DEM, dementia; MCI, mild cognitive impairment; TB, larger than median decrease in Trail B test score.

Covariates: A indicates 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, No. of APOE ε4 alleles; ED, education; FU, follow-up duration; HD, history of heart disease; MRI, brain lesions identified by MRI at baseline; MLK, milk intake; PAD, history of peripheral artery disease; R, race; S, sex; SMK, smoking.

Blood pressure indexes at baseline: DP/SP indicates diastolic (+5 mm Hg)/systolic (+10 mm Hg) blood pressure; DH1/DH2, diastolic blood pressure 90 to 94 mm Hg/≥95 mm Hg; DH1-T/DH2-T, diastolic blood pressure 90 to 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; SH2-E4/SH2+E4, stage 2 systolic hypertension in absence/presence of the APOE ε4 allele.

4).^{35,71-79} Although plagued by low numbers and overexploitation of scarce data, the mainstream of these analyses suggests that diuretics^{71,78} might confer particular benefit in

the prevention of cognitive impairment. All of the nonrandomized longitudinal studies of cognitive function have to be interpreted within the context of their limitations, such as

TABLE 3. Association Between Brain Lesion and Blood Pressure Indexes

Study	Outcome	N	FU, y	Age, y	F, %	CVA,%	BP, mm Hg	Covariates	Effect Size (95% CI)	P
HAAS, 2000 ⁶²	NFTH	243	36.0	53	0	(...)	.../...(...)	A (at death),	[SH2] 1.41 (0.73 to 2.74)	≈0.30
								E4, AHT	[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 ⁶³	WMLS	514	≈20	51	53	...	131/81 (25)	S, A, BMI, SMK, DM	[HT<20] 2.9 (1.5 to 5.8) [HT>20] 2.6 (1.2 to 5.6)	≈0.002 ≈0.01
Rotterdam, 2002 ⁶³	WMLS	563	≈5	69	50	...	137/73 (39)	S, A, BMI, SMK, DM	[HT<5] 1.6 (0.9 to 2.9) [HT>5] 1.8 (1.1 to 3.0)	≈0.11 ≈0.02
Rotterdam, 2003 ⁶⁴	CAS	434 79	20	51	53	...	131/81 (...)	S, A, SMK	[DP-T] 0.08 (0.00 to 0.17) [DP+T] -0.02 (-0.22 to 0.19)	≈0.05 ≈0.89
Goldstein, 2005 ⁶⁵	WMH	121	5.0	66	57	0	119/72 (0)	A	[SP] 1.49 (1.10 to 2.02) [SPA] 1.57 (1.08 to ≈1.70)	0.01 0.02

Abbreviations: N indicates No. 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 CI. “...” represents unavailable information that could not be estimated. Studies were ordered according to age at enrolment.

Study acronym: HAAS indicates Honolulu Asia Aging Study.

End point: CAS indicates cortical atrophy score on MRI of the brain; NFTH/NFTN, count ratio vs normal blood pressure for neurofibrillary tangles in hippocampus/neocortex; NPH/NPN, count ratio vs normal blood pressure for neuritic plaques in hippocampus/neocortex; WMH, white-matter hyperintensities; WMLS, subcortical white matter lesions defined as the upper fifth of the distribution according to severity.

Covariates: A indicates age; AHT, antihypertensive drug treatment; BMI, body mass index; DM, diabetes mellitus; E4, No. of APOE ε4 alleles; S, sex; SMK, smoking.

Blood pressure indexes at baseline: DH2 indicates 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 <5/20 years; HT>5,HT>20, hypertension present for >5 or 20 years; SH2, stage 2 systolic hypertension; SP, systolic blood pressure (+ 10 mm Hg); 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.

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

Study	Outcome	N	Events (Rate per 100)	FU, y	Age, y	F, %	CVA, %	Treated, %	Covariates	Effect Size (95% CI)	P
EVA, 1999 ³⁵	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 ⁷⁶	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 [Cd]					10.6 [Cd]		0.30 (0.07 – 1.25)	0.10
			12 [Cnd]					13.0 [Cnd]		0.82 (0.37 – 1.83)	0.63
Kuopio, 2004 ⁷⁹	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 ⁷²	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 ⁷³	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 ⁷⁴	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
CCS, 2006 ⁷⁸	AD	3217	102 (3.17)	3.2	≈74.1	≈58.2	≈4.2	45.3	S, A, CHL, E4, CVA, HD, DM, ED	0.64 (0.41 – 0.98)	≈0.036
			26 [D]					26.5 [D]		0.61 (0.37 – 0.98)	≈0.037
			5 [Dp]					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 [Cd]					5.8 [Cd]		0.53 (0.16 – 1.34)	≈0.17
			10 [Cnd]					9.2 [Cnd]		1.16 (0.55 – 2.20)	≈0.64
PHRSP, 2005 ⁷⁷	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
			28.3 [D]					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	
Indianapolis, 2002 ⁷⁵	CI	1617	288 (17.8)	≈4.7	77.7	66.5	10.8	46.6	S, A, HD, HT, ED, CSID	0.62 (0.45 – 0.84)	0.002
			28.3 [D]					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	
Kungsholmen, 1999 ⁷¹	DEM	1307	224 (17.1)	3.0	82.5	76.1	≈10.0	44.9	S, A, SBP, CVA, HD, ED	0.7 (0.6 – 1.0)	0.03
			73 [D]					37.0 [D]		0.7 (0.5 – 1.0)	0.02

Abbreviations: N indicates No. of subjects; FU, average follow-up; F, proportion of women; 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 indicates 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; PHRSP, Palmetto Health Richland Senior Primary Care Practice.

Antihypertensive drugs: A indicates angiotensin-converting enzyme inhibitors; C, calcium-channel blockers; Cd, dihydropyridine calcium channel blockers; Cnd, nondihydropyridine calcium channel blockers; D, diuretics; Dp, potassium-sparing diuretics.

End points: CI, cognitive impairment defined as dementia or poor performance on screening and/or repeat cognitive testing; DEM, dementia; MCI, mild cognitive impairment.

Covariates: A indicates 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, No. 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; S/DBP, systolic and diastolic blood pressure.

Effect size: relative risk associated with antihypertensive drug treatment.

reverse causality, patients with more severe hypertension being more likely to be treated, self-selection of patients consenting to follow-up, and the arbitrary nonrandomized definition of the drug class used as reference.

Randomized Clinical Trials

The trial conducted by the Medical Research Council in older adults⁸¹ was the first outcome study that investigated the effects of antihypertensive drug treatment on cognitive func-

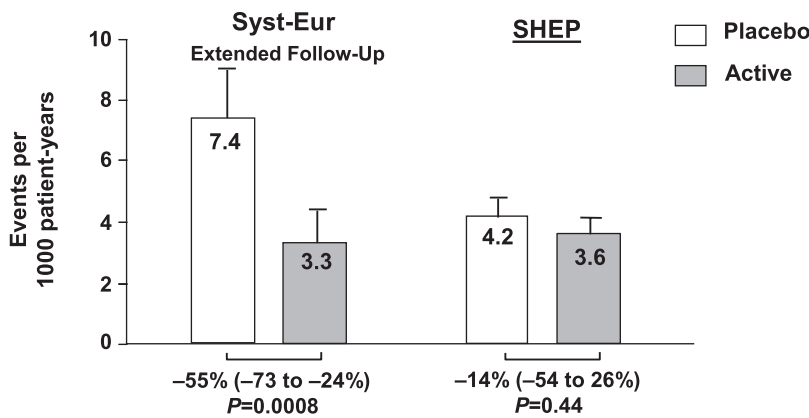


Figure 3. Incidence of dementia in the Systolic Hypertension in Europe Trial (Syst-Eur⁸⁴) and the SHEP^{83,87}. In the Syst-Eur trial, the number of cases of new-onset AD was 29 of 43 and 12 of 21 in the patients randomly assigned to placebo and active treatment, respectively.⁸⁴ The corresponding incidence of vascular dementia was 12 of 43 and 7 of 21.⁸⁴ The SHEP reports^{83,87} did not differentiate between AD and VaD.

tion. The patients were randomly assigned to a diuretic (hydrochlorothiazide plus amiloride), a β -blocker (atenolol), or placebo.⁸¹ Both active treatments reduced blood pressure below the placebo level. Over a period of 54 months, 2584 patients underwent elaborate psychometric tests.⁸¹ No significant differences in the test scores occurred. However, follow-up of 387 surviving Medical Research Council patients for 9 to 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, aging, and alcohol intake.⁸²

The Medical Research Council study,⁸¹ unfortunately, did not report on the incidence of overt dementia. In 4 outcome trials of blood pressure lowering treatment,^{83–86} dementia was a secondary outcome in its own right. The double-blind placebo-controlled Systolic Hypertension in the Elderly Program (SHEP)⁸³ included 4736 patients with a mean age of 72 years. Active treatment consisted of chlorthalidone with the possible addition of atenolol or reserpine. SHEP failed to demonstrate a significant effect of antihypertensive treatment on the incidence of dementia (Figure 3) despite between-group blood pressure differences >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% CI: -26% to 54%; $P=0.44$).⁸³ A subsequent report⁸⁷ 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, nonwhite, randomly assigned 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 toward the null hypothesis of no differences between the treatment groups.⁸⁷

In the double-blind placebo-controlled Systolic Hypertension in Europe 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.¹³ 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 end point of fatal and nonfatal stroke. Of 4695 randomly assigned patients, 2418 participated in the substudy on dementia (mean age: 70 years).¹³

Compared with placebo, active treatment reduced blood pressure by 8.3 mm Hg systolic and 3.8 mm Hg diastolic and the incidence of dementia by 50% from 7.7 to 3.8 cases per 1000 patient-years.¹³ After the double-blind trial had stopped in 1997, all of the 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).⁸⁴ Immediate compared with 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).⁸⁴

In the Perindopril Protection Against Recurrent Stroke Study,⁸⁵ 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 with 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%; $P=0.02$).⁸⁵

The Study on Cognition and Prognosis in the Elderly was set up as a double-blind, placebo-controlled trial in 4964 patients (mean age: 76 years).⁸⁶ 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 randomly assigned to placebo than in those allocated candesartan.⁸⁶ The achieved blood pressure was 3.2/1.6 mm Hg lower in the candesartan group. In a posthoc analysis,⁸⁸ patients with cognitive impairment at baseline (Mini Mental State Examination score: 24 to 28) experienced less further decline in this test on candesartan than in the control group.

Overall, the 4 dementia trials^{83–86} included 18 196 patients and 642 dementia cases. The P value for heterogeneity across trials was not significant ($P=0.18$). 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

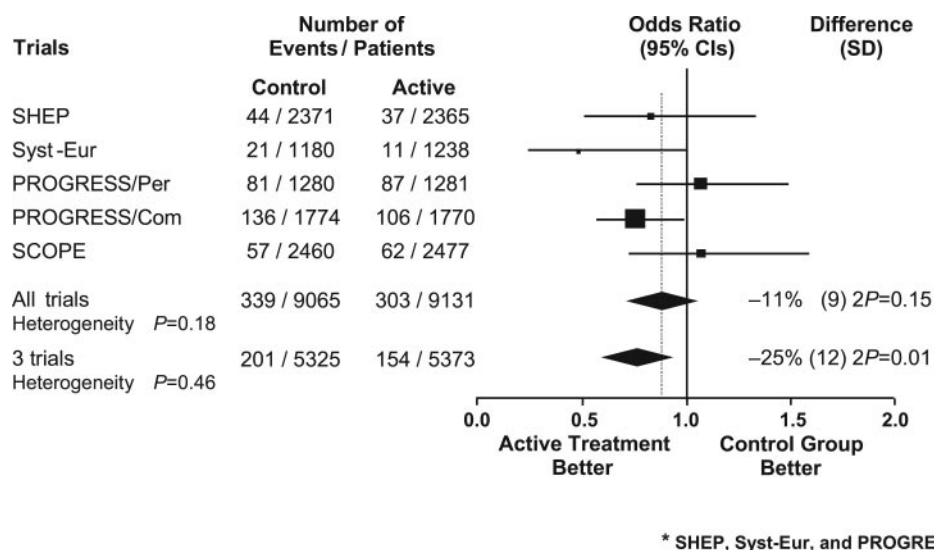


Figure 4. Effects of blood pressure-lowering treatment on the incidence of dementia in placebo-controlled trials. ■, odds ratios in individual trials and have a size proportional to the inverse of the variance of the odds ratios. Horizontal lines and ♦, 95% CIs for individual trials and summary statistics, respectively. Pooled estimates were computed from a fixed-effect model. Three trials refers to SHEP,⁸³ Syst-Eur,⁸⁴ and PROGRESS combined treatment with perindopril and indapamide.⁸⁵ The vertical dotted line marks the position of the point estimate of the pooled effect sizes for all trials combined.

significance ($P=0.15$). 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,⁸³ Systolic Hypertension in Europe,⁸⁴ and the combination therapy arm of Perindopril Protection Against Recurrent Stroke Study⁸⁵ and 1.08 (CI: 0.84 to 1.38; $P=0.54$) for Study on Cognition and Prognosis in the Elderly⁸⁶ and the perindopril-only subgroup of the Perindopril Protection Against Recurrent Stroke Study trial.⁸⁵ The difference between the latter summary statistics was significant ($P=0.04$).

Perspectives and Conclusions

Although hypertension has long been recognized to play a central role in the pathogenesis of VaD, our review underscores that it is an equipotent risk factor for AD. Early treatment of hypertension is an effective way to prevent dementia, including AD. Our review also illustrates that research into dementia requires a comprehensive multidisciplinary approach, in which basic researchers, neurologists, geriatricians, and cardiovascular physicians should join forces. Reviewers and editors can facilitate this process. In scrutinizing submitted research articles, they might adhere to more stringent standards with regard to the diagnostic instruments that have been administered, and they might 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 non-randomized studies, which only provide the lowest level of scientific evidence and which, at best, are hypothesis generating, should be discouraged in favor of prospective surveys and randomized clinical trials, respectively.

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