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The association between blood pressure and cognitive function

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Summary

Longer lifespans have been accompanied by an increasing number of older people suffering from impaired cognitive function (dementia) including Alzheimer's disease (AD) and vascular dementia (VaD). Some studies have suggested that hypertension in old age correlates with the pathogenesis of dementia. Since hypertension is potentially reversible, a number of randomized trials have examined whether antihypertensive treatment may help to prevent dementia. We review five studies, all using subjects aged 60 years or older, which investigated different antihypertensive pharmacological treatments and found conflicting results regarding impact on dementia. At the same time, other studies have suggested that hypotension in older people, especially those with low diastolic blood pressure, are also at higher risk for developing dementia. Four studies are reviewed here, but none is able to determine unequivocally if hypotension is a cause or a consequence of dementia in old age.

Key words: hypertension, hypotension, dementia, cognition, antihypertensive treatment.

Introduction

Although many major causes of death including heart disease and stroke have recently been on the decline, deaths associated with impaired cognitive function (dementia) have been rising dramatically.[1] Many studies have identified common vascular risk factors as markers for the pathogenesis of both Alzheimer's disease (AD) and vascular dementia (VaD), while longitudinal studies have suggested that hypertension is associated with a higher incidence of dementia in old age. It has been observed that long-standing hypertension may lead to severe atherosclerosis and impaired cerebrovascular autoregulation, which in turn is thought to correlate with dementia.[2] For these reasons, several studies have investigated whether antihypertensive treatment may retard cognitive decline or dementia.[3–7] These five randomized controlled trials are reviewed.

At the same time, hypotension in later life may contribute to diminished cerebral perfusion, which can potentially lead to dementia. Consistent with this, some reports have suggested that hypotension, especially low diastolic blood pressure in late life, increases risk.[2] This literature is also reviewed.

Hypertension and the risk of dementia

In general, the risk of hypertension, which is defined as a systolic blood pressure $\geq$ 140 mmHg and/or a diastolic blood pressure $\geq$ 90 mmHg,[8] increases with advancing age. In fact, the prevalence of hypertension in individuals 60 years and older is double that of those aged 49–59 years. Considering that the incidence of dementia among the elderly population is rising rapidly worldwide[9] and evidence is accumulating that hypertension may contribute to the development of both AD and VaD,[10] there is reason to believe effective management of hypertension may translate into major health benefits through protection against dementia.

Can control of hypertension protect against dementia?

Despite the speculated relationship between hypertension and dementia, clinical trials examining the preventive effects of antihypertensive therapy on dementia have been inconclusive (Table 1). Among five randomized double blind placebo-controlled trials surveying antihypertensive treatments and dementia, four (Syst-Eur, PROGRESS, SCOPE and HYVET-COG) used the Mini-Mental State Examination (MMSE), a widely used screening instrument, to assess cognitive function. In the fifth

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Table 1. *Randomized controlled trials about antihypertensive treatments and dementia/cognitive decline*

Study setting	Participants and follow-up	Treatment	Test	Main results
Systolic hypertension in Europe study (Syst-Eur)[3]	2418 systolic hypertensives; mean age 70 years, follow-up 3.9 years	CCB (nitrendipine) with possible addition of ACE-I (enalapril), diuretic (hydro-chlorothiazide), or both *vs*. placebo	MMSE	Mean difference in BP between the placebo and treatment groups was 7.0 mmHg SBP and 3.2 mmHg DBP. Rates of dementia incidence were 7.4 and 3.3 cases per 1000 patient-years (risk reduction 55%; 95% CI: 24–73%), respectively. Significant
The Perindopril Protection Against Recurrent Stroke Study (PROGRESS)[4]	6105 subjects with prior stroke or transient ischemic attack; mean age 64 years, follow-up 3.9 years	ACE-I (perindopril) with possible addition of diuretic (indapamide) *vs*. placebo	MMSE	Mean difference in BP between placebo and treatment groups was 9.0 mmHg SBP and 4.0 mmHg DBP. Rates of dementia incidence were 7.1 and 6.3% (relative risk reduction 12%; 95% CI: –8 to 28%), respectively. Not significant. Rates of cognitive decline were 11.0 and 9.1% (risk reduction 19%; 95% CI: 4–32%), respectively. Significant
Systolic Hypertension in the Elderly Program (SHEP)[5]	4736 systolic hypertensives; mean age 72 years, follow-up 4.5 years	Diuretic (chlorthalidone) with possible addition of beta blocker (atenolol) or sympathetic nervous blocker (reserpine) *vs*. placebo	Short-CARE	Mean difference in BP between placebo and treatment groups was 12 mmHg SBP and 4 mmHg DBP. Rates of dementia incidence were 4.2 and 3.6 cases per 1000 patient-years (relative risk reduction 14%; 95% CI: –26 to 54%), respectively. Not significant
Study on Cognition and Prognosis in the Elderly (SCOPE)[6]	4964 hypertensives; SBP 160–170/DBP 90–99 mmHg; aged 70–89, follow-up 3.97 years	ARB (candesartan) *vs*. placebo; open-label antihypertensive drugs were added to both groups	MMSE	Mean difference in BP between placebo and treatment groups was 3.2 mmHg SBP and 1.6 mmHg DBP; there was no significant difference between the groups in the adjusted change in MMSE score (mean difference 0.15; 95% CI: –0.08 to 0.38). Rates of dementia incidence were 6.8 and 6.3 cases per 1000 patient-years, respectively. Not significant. Rates of cognitive decline were 15.2 and 13.5 cases per 1000 patient-years, respectively. Not significant
Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG)[7]	3336 hypertensives; SBP 160–200 and DBP < 110 mmHg; age = 80, follow-up 2.2 years	Diuretic (indapamide) with possible addition of ACE-I (perindopril) *vs*. placebo	MMSE	Mean difference in BP between placebo and treatment groups was 15 mmHg SBP and 5.9 mmHg DBP. Rates of dementia incidence were 38 and 33 cases per 1000 patient-years (hazard ratio 0.86; 95% CI: 0.67–1.09), respectively. Not significant

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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study (SHEP), cognitive screening was performed by a short-comprehensive assessment and referral evaluation (short-CARE) questionnaire. These five studies are described below.

Syst-Eur

The Systolic Hypertension in Europe study (Syst-Eur) investigated whether antihypertensive treatment in elderly patients with isolated systolic hypertension led to a significant change in stroke morbidity and mortality. Syst-Eur investigated the effects of a calcium channel blocker (CCB; 10–40 mg/day nitrendipine). If necessary, nitrendipine was combined with an angiotensin converting enzyme (ACE)-inhibitor (5–20 mg/day enalapril maleate) and/or a diuretic (12.5–25 mg/day hydrochlorothiazide). Participants had no dementia and were at least 60 years old. Their systolic blood pressure at the beginning of the trial was between 160 and 219 mmHg and their diastolic blood pressure was below 95 mmHg. Antihypertensive therapy began immediately after randomization in the active treatment group, but only after termination of the double-blind trial in the control patients. The mean difference in blood pressure between the control and treatment groups at the end of the trial was 7.0 mmHg systolic and 3.2 mmHg diastolic; the rates of dementia for patients in the control and active treatment groups were 7.4 and 3.3 cases per 1000 patient-years (relative risk reduction 55%; 95% CI: 24–73%), respectively.

In Syst-Eur, because active treatment using a CCB resulted in a 42% decrease in the primary end-point of fatal and non-fatal stroke, only 2418 of the 4695 randomly assigned patients participated in a sub-study on dementia. Compared with the control group, the portion of the treatment group that received only CCB (60%) had a significantly reduced risk of dementia (55%). Interestingly, while the total incidence of dementia was 64 cases, 41 of these were AD. Therefore, Syst-Eur suggests that using a CCB to lower blood pressure may protect against dementia, particularly AD, in elderly individuals with systolic hypertension.

PROGRESS

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a trial involving 6105 patients, all with prior stroke or transient ischaemic attack. Participants were assigned to either active treatment (perindopril for all participants plus indapamide for those with neither an indication nor a contraindication to a diuretic) or a matching placebo(s). The mean difference in blood pressure between the two groups was 9.0 mmHg systolic and 4.0 mmHg diastolic; the rates of dementia in patients in the control and active treatment groups at trial end were 7.1% and 6.3% (relative risk reduction 12%; 95% CI: −8 to 28%). This difference is not statistically significant. However, the rates of cognitive decline were 11.0% and 9.1% (risk reduction 19%; 95% CI: 4–32%), difference, which is significant.

SHEP

The Systolic Hypertension in the Elderly Program (SHEP) study was a trial conducted over an average 5-year follow-up period and involved 16 academic clinics. Among the 447,921 candidates aged 60 years and older screened, 4736 (1.06%) were chosen for the study. Systolic blood pressure at baseline ranged from 160 to 219 mmHg, while diastolic blood pressure was less than 90 mmHg. Participants were randomized into either an active antihypertensive drug therapy or a matching placebo group. Active treatment consisted of 12.5 to 25 mg chlorthalidone for step 1, and 25 to 50 mg atenolol for step 2. If atenolol was contraindicated, 0.05 to 0.10 mg reserpine was used instead. The cohort mean difference in blood pressure between the placebo and treatment groups at study end-point was 12.0 mmHg systolic and 4.0 mmHg diastolic; the rates of dementia for the control and active treatment groups were 4.2 and 3.6 cases per 1000 patient-years (relative risk reduction 14%; 95% CI: −26 to 54%), respectively, a difference that is not statistically significant.

SCOPE

The Study on Cognition and Prognosis in the Elderly (SCOPE) was a prospective study conducted from 1997 to 2002. The study involved 4964 patients aged 70–89 years with systolic blood pressures ranging from 160 to 179 mmHg and/or diastolic blood pressures ranging from 90 to 99 mmHg. Patients were assigned randomly to receive the angiotensin II receptor blocker

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(ARB) candesartan or a placebo, with open-label active antihypertensive therapy added as required (84% of patients in the control group). The mean difference in blood pressure between the placebo and treatment groups was 3.2 mmHg systolic and 1.6 mmHg diastolic at the end of the trial; the rates of dementia for the control and active treatment groups were 6.8 and 6.3 cases per 1000 patient-years, respectively, a difference that is not statistically significant.

In a subgroup analysis of SCOPE performed later, a significant positive effect on some cognitive domains (attention and episodic memory) was reported when using testing methods more sensitive than the MMSE.

HYVET-COG

The Hypertension in the Very Elderly Trial-cognitive function assessment (HYVET-COG) examined antihypertensive medication for patients >80 years of age. Eligible patients had no dementia, their systolic blood pressure at entry was 160–200 mmHg, and their diastolic blood pressure was below 110 mmHg. Participants were randomly assigned to receive 1.5 mg slow release indapamide with the option of 2–4 mg perindopril, or a placebo. The target systolic blood pressure was 150/80 mmHg. Possible new cases of dementia (a fall in the MMSE score to <24 or a drop of three points in 1 year) were assessed by standard diagnostic criteria and expert review. HYVET-COG was the first randomized control study to report the effects of antihypertensive treatment in participants aged 80 years and older, finding a significant decrease in stroke after an average follow-up of 2.2 years, which led to its early termination. This follow-up period may be too short to detect any benefit in preventing dementia.

The mean difference in blood pressure between the treatment and control groups at study end was 15 mmHg systolic and 5.9 mmHg diastolic; the rates of dementia for the control and active treatment groups were 38 and 33 cases per 1000 patient-years (hazard ratio 0.86; 95% CI: 0.67–1.09), respectively, a difference that is not statistically significant.

Of these five studies, only Syst-Eur and PROGRESS showed significant differences in the rate of dementia between the treatment and control groups.

However, when data were combined in a meta-analysis with three other placebo-controlled trials (Syst-Eur, SHEP and PROGRESS),[7] antihypertensive therapy was found to significantly reduce the risk of dementia (HR 0.87; 95%CI: 0.76–1.00, $P = 0.045$). Another study, however, found that combining the antihypertensive therapy results from Syst-Eur, SHEP and SCOPE reduced the risk of dementia by 11% (odds ratio 0.89; 95% CI: 0.69–1.16), an insignificant effect.[13] Therefore, further long-term randomized trials designed especially to assess a link between antihypertensive therapy and cognition as the primary outcome are needed.

Hypotension and the risk of dementia

Some reports have suggested the hypotension may also correlate with dementia (Table 2). The Kungsholmen Project[12] studied a cohort of 1642 subjects aged 75–101 years, among whom 202 were diagnosed with dementia, including 112 with AD. The study found that the incidence of dementia was inversely related to both systolic and diastolic blood pressure and that low blood pressure (≤140/75 mmHg) was related to a higher prevalence of both dementia and AD. The Chicago Health and Ageing Project (CHAP)[13] also showed AD to be significantly more common among subjects with low systolic pressure (<130 mmHg) when compared with a control group with a systolic blood pressure of 130–139 mmHg (odds ratio (OR) = 2.2; 95% CI: 1.2–4.1) and that AD is more common among subjects with low diastolic pressure (<70 mmHg) when compared with a control group with a diastolic pressure of 70–79 mmHg (OR = 1.8; 95% CI: 1.1–3.1).

The Bronx Aging Study,[14] a prospective study, examined 406 community-dwelling elderly individuals over the age of 75 and dementia-free at baseline (1980 to 1983). They were followed at 12- to 18-month intervals for up to 21 years. Over a median follow-up of 6.7 years, 122 subjects developed dementia, and of these 65 were diagnosed with AD. Individuals with a diastolic blood pressure <70 mmHg were twice as likely to develop AD than those whose blood pressure was >90 mmHg. Subjects with persistently low blood pressure for over 2 years also had a higher risk of developing dementia. No association with systolic blood pressure was described, nor was there any

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Table 2. *Studies describing an association between hypotension and dementia*

Authors	Study settings	Participants and follow-up	Outcomes	Main results
Guo *et al.* (1996)[12]	Kungsholmen Project, Sweden	1642 subjects, aged ≥ 75 years, cross-sectional, population-based study	Prevalence and adjusted OR of dementia by blood pressure	Dementia inversely related to both SBP and DBP based on the adjusted OR comparison
Morris *et al.* (2000)[13]	Chicago Health and Ageing Project, USA	378 subjects, aged ≥ 65 years, follow-up 3 years	AD; NINCDS-ADRDA	AD had a correlation with low SBP (<140 mmHg) and low DBP (<70 mmHg)
Verghese *et al.* (2003)[14]	Bronx Aging Study, USA	488 community volunteers, aged ≥ 75 years, mean follow-up 6.7 years	Dementia, AD; diagnosed at consensus conferences	AD had a higher correlation with low DBP (<70 mmHg)

NINCDS-ADRDA, National Institute of Neurological and communicative Disordered and Stroke-Alzheimer's Disease and related Disorders Association; OR, odds ratio.

relationship between low diastolic blood pressure and VaD.

Recently, Molander *et al.*[15] studied the association between low blood pressure and cognition in the very old (over 85 years). This cross-sectional study included 575 individuals with measured systolic and diastolic blood pressures, from which pulse pressure (PP) was calculated. Cognitive function was evaluated using the MMSE. After adjustment for several demographic variables and diagnoses, systolic blood pressure was found to be significantly and non-linearly associated with the MMSE, with both high and low blood pressures associated with lower scores. There was also a positive linear association between PP and MMSE scores, but no association between MMSE and diastolic blood pressure. Overall, participants with dementia were found in general to have lower blood pressure.

Although several reports show a relationship between hypotension and dementia, they do not establish whether this relationship is causal. Consequently, further studies are required.

Orthostatic hypotension and dementia

Orthostatic hypotension (OH), arbitrarily defined as a decrease in SBP ≥ 20 mmHg and/or DBP ≥ 10 mmHg upon standing, is more common in patients suffering from dementia.[16] Recently, Mehrabian *et al.*[17] studied the association between cognitive function and OH in 495 consecutive elderly out-patients, finding an association between the two. The study therefore concluded there is a need for longitudinal studies that are designed to evaluate the nature of this relationship.

The renin–angiotensin–aldosterone system and cognitive function

Blocking the renin–angiotensin–aldosterone system (RAS) is another means that could have benefits in the prevention of dementia,[18] but in a manner independent of blood pressure lowering.[19] A potential neuroprotective effect on focal cerebral ischaemia has been reported by blocking the RAS with an ARB that specifically targets the angiotensin II receptor.[20] Moreover, the Fournier hypothesis proposes that ARB treatment has potential advantages over ACE inhibitor treatment in the prevention of stroke and cognitive impairment because of the lower likelihood of harmful effects like vasoconstriction and proatherothrombogenesis, while at the same time promoting neutral or even potentially beneficial effects like vasodilatation and endothelial modulation.[21,22]

Consistent with this theory, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)[23] and the parallel Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) Trial[24] have reported the effects of the ARB telmisartan,

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a unique angiotensin II receptor blocker with peroxisome proliferator-activated receptor-gamma (PPAR-gamma)-stimulating activity, and the ACE inhibitor ramipril on cognitive function in patients aged 55 years and older with established atherosclerotic cardiovascular disease or diabetes with end-organ damage. In ONTARGET, a 56-month median duration follow-up found cognitive impairment occurred in 652 (8%) of the 7865 patients allocated ramipril, 584 (7%) of the 7797 allocated telmisartan, and 618 (8%) of the 7807 allocated a combination of the two (combination *vs*. ramipril, OR 0.95, 95% CI 0.85–1.07, $P = 0.39$; telmisartan *vs*. ramipril, OR 0.90, CI 0.80–1.01, $P = 0.06$). Corresponding figures for cognitive decline were 1314 (17%), 1279 (17%) and 1240 (17%), respectively (telmisartan *vs*. ramipril, OR 0.97, CI 0.89–1.06, $P = 0.53$; combination *vs*. ramipril, OR 0.95, CI 0.88–1.04, $P = 0.28$). In TRANSCEND, cognitive impairment occurred in 239 (9%) of the 2694 participants allocated telmisartan compared with 245 (9%) of the 2689 allocated a placebo (OR 0.97, CI 0.81–1.17, $P = 0.76$). The corresponding figures for cognitive decline were 454 (17%) and 412 (16%; OR 1.10, CI 0.95–1.27, $P = 0.22$), respectively.

Recently, the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial[25] investigated the impact of ARBs on cognitive function in a randomized controlled design. There were no significant differences in the rate of cognitive decline or dementia between the treatment and control groups. These results were very similar to those found in SCOPE. However, PRoFESS had several limitations that obfuscate its conclusions. For example, the duration of the follow-up period was short, there was a frequent discontinuation of the study drug among subjects, and many patients experienced recurrent stoke requiring termination of the antihypertensive treatments.

Figaro *et al.*[26] reported that antihypertensive therapy with an ARB and diuretic (telmisartan and hydrochlorothiazide) caused significant improvement in cognitive function compared with therapy using an ACE-I and diuretic (lisinopril and hydrochlorothiazide). In addition, the Observational Study on Cognitive function And Systolic Blood Pressure Reduction (OSCAR), an open label trial in 28 countries designed to evaluate the impact of the ARB eprosartan on cognitive function, found that reduction in systolic blood pressure had an independent negative association with cognitive decline (OR 0.77; 95% CI: 0.73–0.82). Recently, Tsukuda *et al.*[27] demonstrated that a low dose of telmisartan had a preventive effect on cognitive decline in an AD mouse model (Aβ-injection mouse model). This was in part due to the clearance of Aβ in response to an inhibition of inflammation because of PPAR-gamma activation. Thus ARBs that can act as a partial agonist for PPAR-gamma may provide a benefit for the treatment of dementia, along with their already well-described blood pressure lowering effects.

Conclusion

It is thought that a dependent relationship exists between the occurrence of hypertension and the risk of developing dementia in old age.[2] This offers promise in the prevention of dementia because hypertension is a potentially reversible risk factor. In particular, given that Syst-Eur found treating hypertension with the dihydropyridine CCB nitrendipine reduced the incidence of AD by 55%, nitrendipine could prove to be a potentially reliable option for protection against dementia.

Hypotension also showed a correlation with dementia in elderly subjects, especially those with diastolic blood pressures $\leq$ 70 mmHg. However, further studies are required to determine whether this relationship is causal or a secondary response to neurodegeneration that affects blood pressure centres within the brain.

As for AD, because current theories assume AD is triggered by the accumulation of soluble and insoluble forms of β-amyloid, if high or low blood pressure can increase the risk of AD, they should then also lead to an accumulation of β-amyloid.

Therefore, future trials primarily designed to investigate the effects of antihypertensive and antihypotensive agents on impaired cognition are needed. In particular, whether these agents possess specific neuroprotective properties or exert their effects by an increase in cerebral perfusion remains to be clarified.

Conflicts of interest

The authors declared no conflicts of interest.

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