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REVIEW PAPER

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High blood pressure in dementia: How low can we go?

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Abstract

Hypertension is an important public health concern. The prevalence keeps increasing, and it is a risk factor for several adverse health outcomes including a decline in cognitive function. Recent data also show that the prevalence of hypertension and

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age-related dementia is rising in Asian countries, including in the oldest old group. This study aims to discuss possible treatments for high blood pressure in the elderly and propose an optimal target for BP relative to cognitive outcomes. This review discusses several studies on related blood pressure treatments that remain controversial and the consequences if the treatment target is too low or aggressive. Longitudinal, cross-sectional, and RCT studies were included in this review. An optimum systolic blood pressure of 120-130 mm Hg is recommended, especially in nondiabetic hypertensive patients with significant risk factors. In the oldest old group of patients, hypertension might have a protective effect. The use of calcium channel blockers (CCB) and angiotensin receptor blocker (ARB) is independently associated with a decreased risk of dementia in older people. However, personalized care for patients with hypertension, especially for patients who are frail or very old, is encouraged.

1 | INTRODUCTION

The relationship between arterial hypertension and impairment of cognition is important since the prevention of hypertension, early intervention, and adequate control of blood pressure could modify the current high prevalence and global incidence of mild cognitive impairment (MCI) and dementia.[1]

Hypertension is an important public health concern. Its prevalence keeps increasing, and it is a risk factor for several adverse health outcomes (CHD, stroke, heart failure, CKD, and a decline in cognitive function).[2] Approximately 365 million people in Asia were classified as elderly in 2017. This number is rising and expected to reach approximately 520 million by 2030. The risk of hypertension and cognitive impairment/dementia increases with age.[3]

Recent data also show that the prevalence of hypertension and age-related dementia is increasing in Asian countries.[4,5] Furthermore, dementia in the oldest old group is also considered a growing public health issue.[6]

Patients with uncontrolled hypertension have a higher risk of developing not only stroke and heart disease but also dementia.[7] Although less evidence has been found between late-life blood pressure (BP) and cognitive decline, many studies, especially longitudinal studies, have consistently shown that hypertension, especially in midlife, is a risk factor for cognitive decline and dementia.[7-9] However, the necessity of blood pressure treatment remains controversial.[7,10] This study aims to discuss possible treatments for high blood pressure in the elderly and how to assign an optimal target for lower BP relative to cognitive outcomes.

2 | THE EVIDENCE FROM OBSERVATIONAL STUDIES

From longitudinal studies, we already know that the treatment and control of hypertension protects against dementia.[8,11] However, the cutoff for the lowest BP as a treatment target remains controversial, including the optimal target when lowering BP for the prevention of dementia and regarding the class of drugs that may have neuroprotective effects.

The evidence in several studies is mixed, including results that show a significant association between high BP and worsening cognitive function, no association, a U-shaped association, or even the opposite association.[10,12-14] One large study—the Framingham Heart Study—also reported no significant association between late-life BP and cognitive function.[15]

Other longitudinal studies have shown an association between reduced cognitive function on processing speed and verbal memory and elevated BP in midlife, defined as a systolic BP (SBP) of 120-139 mm Hg and diastolic blood pressure (DBP) of 80-89 mm Hg.[16] However, a few other studies reported either no association or a U-shaped association, which is an elevated risk at lower and higher BP, between hypertension in midlife and cognition in late life.[10,12-14,17]

A systematic review was performed by Sharp et al to explore whether hypertension is associated with the incidence of vascular dementia (VaD).[18] Eleven studies fulfilled the inclusion and exclusion criteria, with 6 cohort studies and 5 cross-sectional studies, which included 425 patients with VaD and 7698 control subjects in cohorts studies, and 343 VaD and 2159 control in cross-sectional studies. Prevalence studies reported a significant relationship between hypertension and an increased risk of VaD, with an odds ratio (OR) of 4.84. The incidence of VaD showed an OR of 1.59.[18]

In this systematic review, the OR in prevalence studies was more than three times greater than that obtained from incidence studies (1.59:4.84), and since the average age of the VaD patients was significantly higher than that of the control group in the prevalence study, these result indicate that age is a likely risk factor for VaD (Table 1).[18]

The Hisayama Study was conducted in 1988, with 682 residents aged 65 to 79 years enrolled in the study, and it investigated the association between midlife and late-life BP with the risk of dementia.[19] After adjusting for potential confounding factors, including age, sex, education level, use of antihypertensive agents,

TABLE 1 Clinical trial of hypertension and dementia

Study	Study Setting/ Population	Measurement	Groups	Intervention	Results
Systolic Hypertension in Europe study (SYST-EUR) [37,38]	Europe. Nondemented patients aged 60 y old or more with SBP 160-219 mm Hg, DBP below 95 mm Hg	MMSE measurement was 23 or less	Placebo (n = 1180) and active treatment group (n = 1238)	Nitrendipine (10-40 mg/d) Possible addition of enalapril (5-20 mg/d) Hydrochlorothiazide (12.5-25 mg/d) 2-3.9 y follow-up	Antihypertensive treatment (long-acting dihydropyridine) lower dementia incidence in old patients with systolic hypertension. Dementia were reduced 55% from 7.4 to 3.3 cases per 1000 patient-years (43 vs 21 cases, $P < .001$, 95% CI, 24%-73%)
PROGRESS (Perindopril Protection against Recurrent Stroke Study)[39,50]	From 172 centers in Asia, Australasia, and Europe were randomly. 6105 participants with mean age of 60 with prior stroke or transient ischemic attach within the past 5 years. 40% of Asian participants, taken from Japan and China (1176 underwent active treatment and 1176 placebo)	MMSE measurement was 24 or less	Placebo (n = 3054) and active treatment (n = 3051)	Perindopril 3.8 y follow-up	Rates of cognitive decline were different significantly between treatment and control group (9.1% vs 11%) with 19% risk reduction ($P = .01$, 95% CI, 4-32%)
Systolic Hypertension in the Elderly Program (SHEP) study[40]	16 clinical centers in the United States. 4736 participants with 60 years of age or older with SBP 160-219 mmHg, DBP below 90 mmHg	Short-Comprehensive Assessment and Referral Evaluation (short-CARE)	Placebo (n = 2210) and active treatment (n = 2246)	Step 1 drug = chlorthalidone 12.5-25 mg/d Step 2 drug = atenolol 25 mg/d or reserpine 0.05 mg/d 4.5 years follow-up	Rates of dementia in active treatment group compared to control were statistically significant. (3.6 vs 4.2 cases per 1000 patient-years) with 14% risk reduction (95% CI, −26%-54%)
SCOPE (the study on cognition and prognosis in the elderly) [41,42]	A total of 527 centers in 15 countries, mainly in Europe, participated in the study. 4964 elderly patients age 70-89 y old with SBP 160-179 mm Hg, or DBP 90-99 mm Hg	MMSE reduction of 4 points or more	Placebo (n = 2477) and active treatment (n = 2460)	Angiotensin receptor blocker candesartan 8 mg 3.7 years follow-up	The rates of dementia between treatment and control were statistically significant (6.3 vs 6.8 cases per 1000 patient-years) ($P > .2$).
HYVET COG (Hypertension in the Very Elderly Trial) [43]	HYVET recruited participants from Eastern and Western Europe, China, Australasia, and Tunisia. 3336 elderly patients age 70-89 y with SBP >160 mm Hg, DBP <90 mm Hg. (Chinese participants accounted for 40% of all patients)[51]	MMSE score 24 or less	Placebo (n = 1649) and active treatment (n = 1687)	Hydrochlorothiazide 12.5 mg 2.2 y of follow-up	Mean MMSE score fell higher in the control group compared to candesartan group, but the results were not different statistically. (Hazard ratio 0.86, 95% CI, 0.67-1.09)

(Continues)

TABLE 1 (Continued)

Study	Study Setting/ Population	Measurement	Groups	Intervention	Results
SPRINT MIND[46]	102 sites in the United States and Puerto Rico among adults aged 50 years or older with hypertension but without diabetes or history of stroke. Among 9361 randomized participants (mean age, 67.9 years; 3332 women [35.6%]), 8563 (91.5%) completed at least 1 follow-up cognitive assessment	For white participants scoring lower than 19 (with < 12 y of education) or lower than 21 (with ≥ 12 y of education) on the MoCA, nonwhite participants scoring lower than 17 (with < 12 y of education) or lower than 19 (with ≥ 12 y of education) on the MoCA, or any participant with a decrease of 5 or more points from a previous MoCA assessment,	Participants were randomized to a systolic blood pressure goal of either less than 120 mm Hg (intensive treatment group; n = 4678) or less than 140 mm Hg (standard treatment group; n = 4683).	The median intervention period was 3.34 y with total median follow-up of 5.11 y SBP goal of less than 120 mm Hg (intensive treatment group; n = 4678) or an SBP goal of less than 140 mm Hg (standard treatment group; n = 4683).	Adjudicated probable dementia occurred in 149 participants in the intensive treatment group vs 176 in the standard treatment group (7.2 vs 8.6 cases per 1000 person-years; hazard ratio [HR], 0.83; 95% CI, 0.67-1.04). Intensive BP control significantly reduced the risk of mild cognitive impairment (14.6 vs 18.3 cases per 1000 person-years; HR, 0.81; 95% CI, 0.69-0.95) and the combined rate of mild cognitive impairment or probable dementia (20.2 vs 24.1 cases per 1000 person-years; HR, 0.85; 95% CI, 0.74-0.97).

diabetes mellitus, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake, the risk of VaD increased progressively with elevated BP levels, but not all elevated BP caused dementia. The hypothesis proposed from the study was that the vascular damages related to hypertension in the brain begin earlier in the life span and gradually become less reversible.[19] In addition, the effects of midlife hypertension to the brain can be seen through arteriosclerosis measurement, including pulse wave velocity.[7] Moreover, midlife hypertension is also a significant predictor of white matter hyperintensity volume progression and worse performance in executive function.[20]

In the Framingham Heart Study (FHS), the risk of cardiovascular disease (CVD) following 10 years of follow-up among persons with SBP 130-139 mm Hg and/or DBP 85-89 mm Hg and SBP 120-129 mm Hg and/or DBP 80-84 mm Hg was significantly higher compared with that of their counterparts with SBP <120 mm Hg and DBP <80 mm Hg.[15]

Atherosclerosis Risk in Communities (ARIC) and Women's Health Initiative (WHI) studies also showed that individuals with SBP of 120-139 mm Hg and/or DBP of 80-89 mm Hg had an increased risk of CV events compared with the risk in persons with SBP <120 mm Hg.[21,22]

A large meta-analysis of data from 61 population-based longitudinal epidemiological studies showed a strong continuous graded relationship between SBP and CVD death risk for all age deciles between 40 and 89 years, independent of other CVD risk factors, beginning at SBP levels of approximately 115 mm Hg.[23]

The newest published research from community-based cohort study in United States showed increased risk of dementia was found in midlife and late-life hypertension group (HR 1.49; 95% CI, 1.06-2.08), and both increased risk of dementia and mild cognitive decline were found in midlife hypertension and late-life hypotension group (HR 1.62; 95% CI, 1.11-2.37) (HR 1.65; 95% CI, 1.01-2.69) compared with midlife and late-life normotension group.[24]

3 | TARGET BP IN THE OLDEST OLD

The effect of hypertension in the group of oldest old (aged 80 or older) from the Leiden 85 plus study showed a 10 mm Hg increase in SBP was associated with better cognitive performance in global tests and several domain-specific tests, independent of cardiovascular risk factors, and heart failure.[25]

Another oldest old study, the Newcastle 85 plus, showed that having high BP defined as SBP/DBP ≥130/85 mm Hg or treatment was associated with better global cognitive function over 5 years.[26] The Vantaa 85 plus study also reported the same result, where lower SBP increased mortality among people aged 85 or more with no significant relationship between baseline BP and dementia occurrence.[27,28]

Studies of the association of high BP with dementia are not consistent and age dependent. Understanding long-term trajectories in

blood pressure of those who do and do not develop dementia can help clarify the issue.

Early antihypertensive use may reduce the extent of this decline, but further research is required to identify the risks and benefits of lowering BP when neurodegenerative processes are at a more advanced stage.

4 | TARGET OF BP IN THE FRAIL AND ELDERLY

Frailty is a common problem in the elderly and affects their cognitive performance and functional abilities.[29] Among faster walkers, those with elevated systolic BP (≥140 mm Hg) had a greater adjusted risk of mortality compared with those without. Among slower walkers, neither elevated systolic nor diastolic BP (≥90 mm Hg) was associated with mortality. In participants who did not complete the walk test, elevated BP was strongly and independently associated with a lower risk of death.[30]

5 | PROGRESSIVE DECLINE IN BP IN EARLY STAGES OF DEMENTIA

Neurodegenerative process affecting brainstem and hypothalamic nuclei could influence arterial pressure regulation and systemic metabolism. Associated systemic changes such as weight loss and increased frailty are secondary to the onset of cardiovascular diseases, for instance myocardial infarction and congestive heart failure can reduce the ability of heart to maintain systemic and cerebral perfusion pressures. Honolulu-Asia Aging Study with 32 years of follow-up showed that those who developed dementia had a greater increase, followed by a greater decrease in SBP, which can be modified with antihypertensive medications.[31]

6 | NEGATIVE EFFECT OF AGGRESSIVE TREATMENT AND EXAGGERATED BLOOD PRESSURE VARIABILITY IN DEMENTIA

Aggressive treatment with antihypertensive medication that leads to hypoperfusion can cause hypoxia and ischemia, which directly affect the incidence of dementia. Low diastolic BP and high SBP may also increase the risk of developing dementia through cerebral perfusion.[32,33]

Another concern involves BP variability. Strict BP lowering would decrease the lowest BP, thereby causing, especially in the elderly, exaggerated BP variability (BPV), extreme dips, and postprandial hypotension.[34,35] BPV was more closely associated with cognitive dysfunction (lower MMSE score) than the mean ambulatory BP (ABP).[36] Even in the elderly hypertensive patients well controlled with low 24-hours BP levels, exaggerated weighted SD of 24-hours BP was closely associated with cognitive dysfunction.[34]

7 | THE EVIDENCE FROM RCT

The Systolic Hypertension in Europe study (SYST-EUR) investigated whether antihypertensive treatment in elderly patients with isolated hypertension led to a significant change in stroke morbidity and mortality. In this study, the effects of calcium channel blocker (CCB) were investigated. Participants who had no dementia and were at least 60 years old showed dementia rates of 3.3 and 7.4 cases per 1000 patient-years in both the intervention groups and control group, respectively, with a significant relative risk reduction of 55%.[37] Interestingly, while the total number of dementia cases was 64, 41 of these showed Alzheimer's disease. Therefore, the results of this study suggest that using CCB to lower BP in the elderly with hypertension may protect against dementia, particularly Alzheimer's disease.[37,38]

A second study—PROGRESS (Perindopril Protection against Recurrent Stroke Study)—involved approximately 6000 patients with prior stroke or TIA. PROGRESS is the only study that has assessed the risk of dementia in patients with stroke. Participants were assigned to either active treatment (perindopril) with or without indapamide or placebo. The rates of dementia between the active treatments and the control group were 6.3% and 7.1%, respectively, but these were not significant. However, the rates of cognitive decline were 9.1% and 11%, which are significant.[39]

A third study—Systolic Hypertension in the Elderly Program (SHEP) study—was a trial conducted over an average 5-year follow-up, with approximately 4700 participants 60 years of age or older, who received active treatment with diuretics as a first step and received the beta-blocker atenolol as a second step, or if contraindicated, reserpine. The rates of dementia in the active treatment group compared with the control were 3.6 and 4.2 cases per 1000 patient-years, respectively, which are insignificant.[40]

The fourth study was a prospective study called SCOPE (the study on cognition and prognosis in the elderly), with approximately 4900 elderly patients age 70 to 89 years, who were randomly assigned to receive candesartan, an angiotensin receptor blocker (ARB), or placebo. The rates of dementia between the treatment and control group were 6.3 and 6.8 cases per 1000 patient-years, which were insignificant. However, in a subgroup analysis of SCOPE performed later, a significantly positive effect on some cognitive domains (attention and episodic memory) was reported when using testing methods more sensitive than MMSE.[41,42]

Finally, the fifth study was HYVET COG (Hypertension in the Very Elderly Trial), which examined antihypertensive medication for patient 80 years old and older. Only patients with no dementia were eligible to participate in the trial, and patients received indapamide or ACEi, with a target of SBP/DBP of 150/80. This is the first study to report the effect of antihypertensive agents in very old participants, finding a significant decrease in stroke after an average follow-up of 2.2 years, which led to early termination. This follow-up period may be too short to detect any preventative effect against dementia. The difference in the rate of dementia was insignificant between the active treatment and the control.[43]

Of these five studies, only two studies, SYST-EUR and PROGRESS, showed significant difference in the rate of dementia between the treatment and control groups. However, if the data from these four studies (SYST-EUR, PROGRESS, SHEP, and HYVET CoG) were combined in meta-analysis, antihypertensive therapy was found to significantly reduce the risk of dementia.[19]

Secondary data were obtained from 3526 community-dwelling older people, age 70-78. CCBs and ARB were independently associated with a decreased risk of dementia. The association of CCBs with dementia was most apparent in participants without a history of CVD and with uncontrolled hypertension.[44]

The SPRINT study included 9400 participants, and SPRINT MIND, which is a continuing 3-year cohort phase after the SPRINT trial ended, is part of the study. This study showed SBP differences between treatment groups with a decrease of 13-6 mm Hg. In 1 year, the mean SBP was 121.4 mm Hg in the intensive treatment group and 136.2 mm Hg in the standard treatment group.

The intervention stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome. The results of this study suggested that the risk of mild cognitive impairment and dementia can be reduced by giving intensive treatment.[45]

The SPRINT study confirmed that targeting a systolic pressure of 120 mm Hg instead of the current target of 140 mm Hg can save lives and reduce the risk of CVD in nondiabetic adults aged 50 years and older with high BP. Two subanalysis datasets (SPRINT MIND and SPRINT Senior at 75 plus) were assessed for cognition and memory.[46]

Participants in the SPRINT trial, who were submitted to magnetic resonance imaging (MRI) (n = 454, 67.4%), showed a lower increase in the volume of white matter lesions in the intensive treatment group (P = .004) after 3.98 years of follow-up.[47] The total brain volume decreased in the intensive treatment and in the standard treatment groups without a significant difference.

In addition to the imaging results, a study conducted by Godin et al showed that the white matter lesion was significantly reduced with adequate hypertension treatment.[48] Brain MRI or computed tomography (CT) may be considered for detecting not only white matter lesions but also for silent brain infarctions, lacunar infarctions, and microbleeds.[49]

8 | CONCLUSION

From the studies we reviewed, the optimum systolic blood pressure target should be 120-130 mm Hg, especially in nondiabetic hypertensive patients with significant risk factors. Any advantages of aggressive treatment that allows BP to reach below 120 mm Hg are still unclear. In the oldest old group of patients, hypertension might have a protective effect. The use of CCB and ARB is independently associated with a decreased risk of dementia in older people. Personalized care for patients with hypertension is recommended, especially in frail and/or very old patients.

CONFLICT OF INTEREST

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