Although hypertension is well known as a cause of vascular dementia (VaD), recent findings highlight the role of hypertension in the pathogenesis of Alzheimer’s disease (AD) as well as mild cognitive impairment (MCI). Mild cognitive impairment (MCI) is regarded as a risk for dementia, and its identification is thought to lead to secondary prevention by controlling the risks for cardiovascular diseases. Recent studies have shown that disruption of diurnal blood pressure (BP) variation was closely associated with cognitive impairment via injury of the small cerebral arteries indicating that long-standing hypertension constitutes a risk of brain matter atrophy or white matter lesions (WMLs). In several clinical trials, BP-lowering with antihypertensive agents was suggested to reduce the risk of dementia or cognitive decline. This review paper focuses on the role of hypertension as a risk factor for cognitive impairment, and summarizes current knowledge on the relationships between ambulatory BP monitoring (ABPM) and cognitive impairment. Finally, an overview of the impact of antihypertensive therapy on dementia prevention is provided.

Keywords: ambulatory blood pressure monitoring; blood pressure; cognitive impairment; dementia; hypertension


Hypertension and Dementia
Michiaki Nagai¹,², Satoshi Hoshide¹ and Kazuomi Kario¹

Although hypertension is well known as a cause of vascular dementia (VaD),¹ recent findings highlight the role of hypertension in the pathogenesis of Alzheimer’s disease (AD). Mild cognitive impairment (MCI) is regarded as a risk for dementia, and its identification is thought to lead to secondary prevention by controlling the risks for cardiovascular diseases. Recent studies have shown that disruption of diurnal blood pressure (BP) variation was closely associated with cognitive impairment.²,³ In several clinical trials, BP-lowering with antihypertensive agents was shown to substantially reduce the risk of dementia or cognitive decline.

This review paper focuses on the role of hypertension as a risk factor for cognitive impairment, and summarizes current knowledge on the relationships between ambulatory BP monitoring (ABPM) and cognitive impairment. Finally, an overview of the impact of antihypertensive therapy on dementia prevention is provided.

CARDIOVASCULAR RISK FACTORS AND DEMENTIA
Dementia was subdivided into AD, VaD, or mixed variants. In spite of the literature on the dichotomy between AD and VaD, new concepts highlight the role of cardiovascular risks in the pathogenesis of AD.

VaD⁴,⁵
VaD can arise from stroke involving brain areas critical for memory processing.⁶,⁷ In the elderly, subcortical small vessel disease is known to be associated with VaD. Exposure of the small brain vessels to higher BP pulsatile pressure and flow leads to microvascular damage⁸ that results in white matter damage, silent lacunae, and cortical disconnection.⁹ Multiple infarction dementia exhibits a stepwise but unpredictable course, depending on the size, localization, and number of ischemic insults.⁷

In a case–control study nested within the Framingham cohort, stroke survivors showed a 2.0–2.8-fold greater risk of dementia than controls.⁹

Alzheimer’s disease⁵,¹⁰,¹¹
The extraneuronal and intraneuronal accumulation of amyloid β-peptide (Aβ) starts a pathogenetic cascade that results in neurotoxicity among AD patients.¹¹ Aβ toxicity starts in the entorhinal cortex, and then involves neurons of other areas. The second histopathological hallmark of AD is neurofibrillary tangles that consist of hyperphosphorylated microtubule-associated protein Tau.¹¹ These tangles aggregate as pairs of filaments, so-called paired helical filaments, that affect the nutrition of axon terminals and dendrites.

Mechanism underlying the relationship between cardiovascular disease risk and cognitive impairment⁵
Neuroimaging¹² and postmortem histopathological¹³ studies indicate that up to one-third of AD patients have some degree of vascular pathology, and whereas AD lesions are also present in a similar proportion of VaD.

Cholinesterase inhibitors treatments stimulate regional cerebral blood flow (CBF) in patients with AD or VaD.¹⁴ Aβ constricts human cerebral arteries.¹⁵ Aβ attenuates endothelium-mediated dilatation in the cerebral arteries by production of reactive oxygen radicals and impairs the increase in neocortical CBF in response to somatosensory activation.¹⁶ Transgenic mice overexpressing mutated forms of amyloid
precursor protein, from which misfolded Aβ originates, show a reduction in CBF\(^{15,16}\) and an impaired autoregulation of the cerebral circulation.\(^{17}\) The APOE\(\varepsilon\)4 allele plays a critical role in plaque formation.\(^{18}\) Staessen et al. summed up these pathophysiological overlaps and interactions between AD and VaD.\(^{5}\) In the present review, we focus on the relationship between hypertension and components of AD, and consider the factors shared in common by AD and VaD (Figure 1).

**Figure 1 | Common pathophysiology for VaD and AD. Each of vascular and cholinergic factor is associated with reduced cerebral blood flow. This would be act as a common factor for silent brain injury such as leukoaraiosis or brain atrophy. AD, Alzheimer’s disease; VaD, vascular dementia.**

### HYPERTENSION, DEMENTIA, AND COGNITIVE DECLINE

#### High BP and dementia (VaD and AD)

Several longitudinal cohort studies\(^{5}\) have reported an independent association between BP and dementia. However, the results in the relationship between BP and dementia among these studies were not consistent, presumably due to the differences in age, race, and BP classification. Here, we summarized the prospective studies that investigated the relationship between high BP and dementia (Table 1).\(^{19–25}\) Except for the report by Luchsinger et al.,\(^{24}\) high systolic BP and/or diastolic BP (SBP/DBP) were risk factors for dementia incidence.

In the Framingham Heart Study,\(^{26}\) DBP was shown to increase until the sixth decade of life, then decline due to increasing age-related large artery stiffness, whereas SBP rises steadily from the third through the eighth decade. Higher pulse pressure (PP) was revealed to be a risk for cardiovascular disease.

In the Kungsholmen study,\(^{27}\) the relationship between PP and incidence of dementia was investigated in 1,270 nondemented subjects aged ≥75 years. Dementia was detected with the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition. During the median 4.7 years of follow-up, 339 subjects developed dementia, including 256 AD cases. In comparison with the median tertile of PP (70–84 mm Hg), subjects with higher PP had a significant adjusted relative risk of 1.4 (95% confidence interval (CI): 1.0–2.0) for AD and a nonsignificant adjusted relative risk of 1.3 (95% CI: 0.9–1.7) for dementia. The corresponding figures related to lower PP were 1.7 (95% CI: 1.2–2.3) for AD and 1.4 (95% CI: 1.0–1.9) for dementia. This association was particularly pronounced among women. There was a U-shaped relationship between level of PP and incidence of AD and all dementias.

Higher PP is associated with increased risk for AD and dementia in the elderly, and is suggested to be caused by arterial stiffness and severe atherosclerosis. Poor cerebral perfusion may explain the association between lower PP and increased risk for dementia.

#### High BP and cognitive impairment

**Cognitive impairment.** Several cross-sectional\(^{28}\) or longitudinal cohort\(^{5}\) studies have reported an independent association between BP and cognitive function.

The results in the relationship between BP and cognitive impairment among these studies were not consistent, presumably due to the differences in age, race, severity of risks for cardiovascular disease, cognitive tests, and BP classification. We summarized the studies that investigated the relationship between high BP and cognitive impairment (Table 2).\(^{29–39}\) Except for the report by Guo et al.\(^{31}\) and Cacciato et al.,\(^{32}\) high SBP and/or DBP were risk factors for cognitive impairment.

**MCI.** MCI is a recently described syndrome that is thought to constitute a transition phase between healthy cognitive aging and dementia. The original criteria for MCI\(^{40}\) are outlined as follows: (i) memory complaint, preferably qualified by an informant; (ii) memory impairment for age; (iii) preserved general cognitive function; (iv) intact activities of daily living; (v) not demented. The neuropsychological profile allows mainly two subtypes of MCI to be distinguished: (i) amnestic type MCI (including memory impairment), which may progress preferentially to AD; (ii) multiple domain type MCI (including nonmemory cognitive domains impaired), which may progress to AD and also to VaD, or may even represent a cognitive aging process qualified as normal.\(^{40}\) Risks for cardiovascular disease such as hypertension are suggested to be associated with MCI.\(^{41}\)

In the Women’s Health Initiative Memory Study (WHIMS),\(^{42}\) the cognitive function of 7,149 women aged ≥65 was assessed using the modified mini-mental state examination (MMSE). During a mean follow-up period of 4.5 years, women without
Hypertension tended to have slightly higher modified mini-mental state scores than those with hypertension. Women with hypertension also appeared to be at greater risk for dementia or MCI (hazard ratio (HR): 1.35; 95% CI: 1.07–1.70), although this association was no longer significant when potential confounders were accounted for.

In a cross-sectional study in Kolkata, the prevention and potential risk of MCI were investigated in 960 nondemented and nondepressed subjects. The overall prevalence of MCI was 14.9% (95% CI: 12.2–18.0). The prevalence of the amnestic type was 6.0% (95% CI: 4.4–8.1) and that of the multiple domain type was 8.9% (95% CI: 6.8–11.3). After adjustment for confounders, the amnestic type was more common among men, and the multiple domain type was more common among women with advancement of age. Hypertension and diabetes mellitus were the major risk factors for both types of MCI.

In a prospective study in northern Manhattan, 918 subjects without prevalent MCI at baseline were enrolled to examine whether hypertension is associated with MCI. Among these, 62.8% had hypertension, and use of antihypertensive medication was reported by 394 subjects (42.9%). There were 160 cases of the amnestic type MCI, and 174 cases of multiple domain type MCI during the 4,337 person-years of follow-up. Hypertension was associated with an increased risk of all-cause MCI (HR: 1.40; 95% CI: 1.06–1.77) for severe high DBP, and 4.3 (1.7–10.8) for high DBP; the risk for dementia was 4.8 (2.0–11.0) in those with severe high SBP. BP was not associated with the risk for dementia in treated men.

Based on these studies, hypertension is associated with the subsequent development of MCI. In the future literature, it should be investigated whether the prevention as well as treatment of hypertension may have a beneficial role in reducing the risk for MCI.

### Table 1 | High blood pressure and dementia

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Blood pressure classification</th>
<th>Outcome</th>
<th>Follow-up period</th>
<th>Results (odds ratio or relative risk; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Launer et al.19</td>
<td>3,703 Japanese-American men; never treated hypertensives 57%</td>
<td>DBP; severe high (≥95 mm Hg); high (90–94 mm Hg); normal (80–89 mm Hg); SBP; severe high (≥160 mm Hg); high (140–159 mm Hg); normal (110–139 mm Hg)</td>
<td>Dementia</td>
<td>27 (years)</td>
<td>Among those never treated, the risk for dementia was 3.8 (1.6–8.7) for severe high DBP, and 4.3 (1.7–10.8) for high DBP; the risk for dementia was 4.8 (2.0–11.0) in those with severe high SBP. BP was not associated with the risk for dementia in treated men</td>
</tr>
<tr>
<td>Kivipelto et al.20</td>
<td>1,449 subjects; age 65–79</td>
<td>High SBP ≥ 160 mm Hg</td>
<td>Dementia</td>
<td>21 (years)</td>
<td>The risk for dementia was 2.3 (1.0–5.5) for high SBP</td>
</tr>
<tr>
<td>Kivipelto et al.21</td>
<td>1,449 subjects; age 65–79</td>
<td>High SBP ≥ 160 mm Hg</td>
<td>AD</td>
<td>21 (years)</td>
<td>The risk for AD was 2.6 (1.1–6.6) for high SBP</td>
</tr>
<tr>
<td>Posner et al.22</td>
<td>1,259 subjects; age ≥ 65</td>
<td>N/A</td>
<td>AD, VaD</td>
<td>7 (years)</td>
<td>A history of hypertension was not associated with an increased risk for AD (0.9, 0.7–1.3), but was with an increased risk for VaD (1.8, 1.0–3.2)</td>
</tr>
<tr>
<td>Kivipelto et al.23</td>
<td>1,449 subjects; age 65–79</td>
<td>High SBP &gt; 140 mm Hg</td>
<td>Dementia, AD</td>
<td>21 (years)</td>
<td>High SBP was a significant risk for dementia (1.97, 1.03–3.77); no significant risk for AD (1.57, 0.78–3.14)</td>
</tr>
<tr>
<td>Luchsinger et al.24</td>
<td>1,138 subjects; mean age 76.2</td>
<td>N/A</td>
<td>AD</td>
<td>5.5 (years)</td>
<td>Hypertension was not significantly associated with an increased risk for AD (1.4, 0.9–2.1)</td>
</tr>
<tr>
<td>Li et al.25</td>
<td>2,356 subjects; age ≥ 65</td>
<td>DBP; borderline-high (80–89 mm Hg); normal (&lt;80 mm Hg), SBP; high (≥160 mm Hg); normal (&lt;140 mm Hg)</td>
<td>Dementia</td>
<td>8 (years)</td>
<td>Within the youngest age group (65–74), a greater risk for dementia was found in participants with high SBP (1.60, 1.01–2.55) or borderline-high DBP (1.59, 1.07–2.35) than for those with normal BP</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; VaD, vascular dementia.
### Table 2 | High blood pressure and cognitive impairment

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Blood pressure classification</th>
<th>Neuropsychological test</th>
<th>Follow-up period</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starr et al.29</td>
<td>598 subjects; no antihypertensive treatment; age ≥ 70</td>
<td>Mean 160/86 mm Hg, high (&gt;1 s.d. above mean); medium (within 1 s.d. of mean); low (&gt;1 s.d. below mean)</td>
<td>MMSE</td>
<td>(−) (case–control study)</td>
<td>Significant lower cognitive function in patients with high SBP and DBP</td>
</tr>
<tr>
<td>Kuusisto et al.30</td>
<td>744 subjects; stroke-free; nondiabetic; mean age 73</td>
<td>BP ≥ 160/95 mm Hg or on antihypertensive treatment</td>
<td>MMSE, TMT, BSR HVR, VFT</td>
<td>(−) (case–control study)</td>
<td>Significant lower cognitive function in patients with high SBP and DBP</td>
</tr>
<tr>
<td>Guo et al.31</td>
<td>1,736 subjects; age ≥ 75</td>
<td>Four groups (SBP &gt; 180, 160–179, 130–159, &lt;130 mm Hg)</td>
<td>MMSE</td>
<td>(−) (case–control study)</td>
<td>Positive correlation of cognitive function with SBP and DBP</td>
</tr>
<tr>
<td>Cacciatore et al.32</td>
<td>1,106 subjects; stroke-free; age 65–95</td>
<td>N/A</td>
<td>MMSE</td>
<td>(−) (cross-sectional design)</td>
<td>Positive correlation between cognitive function and DBP</td>
</tr>
<tr>
<td>Kilander et al.33</td>
<td>999 subjects; age 69–75</td>
<td>N/A</td>
<td>MMSE, TMT</td>
<td>20 (years)</td>
<td>High DBP at age predicted impaired cognitive function at age 70; cross-sectional measurement at age 70 showed that high 24-h DBP was associated with lower cognitive function</td>
</tr>
<tr>
<td>Seux et al.34</td>
<td>2,252 subjects; age ≥ 60</td>
<td>SBP 160–219 mm Hg (systolic hypertension)</td>
<td>MMSE</td>
<td>(cross-sectional design)</td>
<td>Negative correlation between cognitive function and SBP</td>
</tr>
<tr>
<td>Suhr et al.35</td>
<td>2,727 subjects; age 20–59</td>
<td>N/A</td>
<td>Symbol digit, serial digit learning, visuomotor reaction time</td>
<td>(−) (cross-sectional design)</td>
<td>Higher SBP was associated with poorer cognitive performance in subjects younger than 40 years</td>
</tr>
<tr>
<td>Elias et al.36</td>
<td>529 subjects; two age groups (18–46 years and 47–83 years)</td>
<td>N/A</td>
<td>WAIS</td>
<td>20 (years)</td>
<td>Higher levels of baseline SBP and DBP were significantly associated with decline in visualization/fluid abilities in both younger and older age groups</td>
</tr>
<tr>
<td>Waldstein et al.37</td>
<td>847 subjects; stroke-free; age ≥ 60</td>
<td>N/A</td>
<td>WAIS, BVRT, TMT A and B</td>
<td>11 (years)</td>
<td>Cognitive decline was apparent among older (80 years) individuals with higher systolic BP; cross-sectional findings indicated moderated U- and J-shaped relations between BP and cognitive function</td>
</tr>
<tr>
<td>Robbins et al.38</td>
<td>147 African-Americans, 1,416 Caucasians; age &lt; 80</td>
<td>N/A</td>
<td>WAIS</td>
<td>(cross-sectional design)</td>
<td>SBP and DBP were significantly negatively associated with cognitive performance for both racial cohorts but were generally of higher magnitude for the African-American cohort</td>
</tr>
<tr>
<td>Obisesan et al.19</td>
<td>6,163 subjects; age ≥ 60</td>
<td>N/A</td>
<td>Short-portable MMSE</td>
<td>(−) (cross-sectional design)</td>
<td>Severe hypertension group had the poorest performance in all age groups except the very old (≥80)</td>
</tr>
</tbody>
</table>

BP, blood pressure; BSR, Buschke selective reminding test; BVRT, Benton visual retention test; DBP, diastolic blood pressure; HVR, Russell’s adaptation of the visual reproduction test; MMSE, mini-mental state examination; SBP, systolic blood pressure; TMT, trail making test; VFT, verbal fluency test; WAIS, Wechsler adult intelligence scale.
that ambulatory BP (ABP) variation is associated with cognitive function. High nocturnal SBP level,\textsuperscript{48} nondipper status,\textsuperscript{49} and exaggerated BP variability\textsuperscript{2} are all suggested to be significant determinants of cognitive impairment. White matter lesion (WML) or brain atrophy is suggested to serve as a substantial pathophysiology.

### WML

Diminished nocturnal BP dip has been observed in patients withBinswanger disease.\textsuperscript{50} Additionally, high-ambulatory SBP level or exaggerated ABP variability has been associated with progression of WML,\textsuperscript{51} although other studies failed to find such an association.\textsuperscript{52}

In the sibships of subjects in the Genetic Epidemiology Network Of Arteriopathy (GENOA) study, both SBP and DBP over 24 h and during the waking and sleeping periods were significantly positively associated with leukoaraiosis volume in African-Caribbeans, whereas both nocturnal SBP and DBP dipping were significantly negatively associated with leukoaraiosis volume among the Caucasians.\textsuperscript{53} Among the hypertensives, the African-Caribbeans had significantly higher 24-h SBP and DBP levels, greater parieto-occipital leukoaraiosis volume, and poorer performance on executive function and verbal fluency than the Caucasians.\textsuperscript{54}

### Brain atrophy

Brain atrophy as assessed by magnetic resonance imaging has been shown to be present essential hypertensives.\textsuperscript{55} In addition, 24-h SBP has been shown to be an independent determinant for brain atrophy in the elderly without any history of hypertension.\textsuperscript{56}

In the Jichi Medical School ABPM Study, Wave 2 Core, we performed ABPM and brain magnetic resonance imaging in 55 elderly hypertensives not treated with antihypertensive medication.\textsuperscript{3} Cognitive function was assessed with MMSE. According to the tertiles of MMSE score, total brain matter volume was significantly different among the groups. In particular, the low MMSE score group had significantly lower total brain matter volume than the high-MMSE score group. In this population, sleep SBP was more significantly negatively associated with total brain matter volume than was either 24 h or awake SBP in multiple linear regression analysis adjusted for age, sex, and body mass index.\textsuperscript{3}

Diurnal BP variation disruption, specifically sleep period, was associated with WML and brain atrophy, which would serve as a pathophysiology for cognitive impairment or dementia.

### BP REDUCTION FOR THE RISK OF COGNITIVE IMPAIRMENT

It is a clinically relevant issue whether BP reduction with antihypertensive agents can influence the incidence of cognitive impairment or overt dementia. Nonrandomized observational studies such as the Rotterdam study,\textsuperscript{1} Cache County Study (CCS),\textsuperscript{57} Indianapolis study,\textsuperscript{58} and Kungsholmen study\textsuperscript{59} have shown that antihypertensive treatment prevented a decline in cognitive function or incidence of dementia. Intriguingly, in the CCS, antihypertensive treatment was associated with reduced incidence of AD. From this standpoint, it would be interesting to investigate which class of antihypertensive agents has the most beneficial impact on our cognitive function.

Several completed randomized controlled clinical trials of BP-lowering agents have reported the effects of treatment on the risk of cognitive impairment or dementia (Table 3).

### Diuretics

In the Medical Research Council’s (MRC) study,\textsuperscript{60} the Systolic Hypertension in the Elderly Program (SHEP) cohort,\textsuperscript{61} and the Hypertension in the Very Elderly Trial Cognitive Function Assessment (HYVET-COG),\textsuperscript{62} the impact of diuretics on cognitive function was evaluated in randomized controlled design. In all the three studies, there were no significant differences in the rate of cognitive decline or dementia between active treatment group and control group. In the HYVET-COG study,\textsuperscript{62} according to the early termination of the trial, the follow-up period may have been too short to detect a difference on the incidence of dementia.

Additionally, in the nonrandomized study of the CCS, diuretics (adjusted HR: 0.57; 95% CI: 0.33–0.94), specifically potassium-sparing diuretics (adjusted HR: 0.26; 95% CI: 0.08–0.64), are associated with reduced incidence of AD.\textsuperscript{57}

### Calcium channel blockers

In the Systolic Hypertension in Europe (Syst-Eur) trial,\textsuperscript{63} median follow-up lasted only 2 years. The trial had to be stopped prematurely, because active treatment of calcium channel blocker (CCB) resulted in a 42% decrease in the primary end point of fatal and nonfatal stroke. Of 4,695 randomly assigned patients, 2,418 participated in the substudy on dementia.\textsuperscript{64} The 60% of the treatment group received CCB alone. Compared with the control group, antihypertensive therapy significantly reduced the risk of dementia by 55%. Interestingly, while the total incidence of dementia was 64 cases, 41 had AD. These findings suggest that BP-lowering therapy initiated with a CCB would protect against dementia, particularly AD, among the elderly with systolic hypertension.\textsuperscript{64}

### Angiotensin-converting enzyme inhibitors

In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)\textsuperscript{65} and the Heart Outcomes Prevention Evaluation (HOPE) study,\textsuperscript{66} the impact of angiotensin-converting enzyme inhibitors (ACE-Is) on cognitive function was evaluated in randomized controlled design. In both
The table below summarizes randomized controlled trials about antihypertensive treatments and dementia/cognitive decline:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Treatment</th>
<th>Neuropsychological test</th>
<th>Follow-up period</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC60</td>
<td>2,584 subjects; aged 65–74; SBP 160–209/DBP &lt; 115 mm Hg</td>
<td>Diuretic (hydrochlorothiazide), β blocker (atenolol) vs. placebo</td>
<td>PALT, TMT-A</td>
<td>4.5 (years)</td>
<td>Significant difference in the mean SBP fall between groups: diuretic 33.5, β blocker 30.9, placebo 16.4 mm Hg; no difference in the mean learning test coefficients (rate of change of score over time) between groups: diuretic −0.31 (95% CI −0.23 to −0.39), β blocker −0.33 (−0.25 to −0.41), placebo −0.30, (−0.24 to −0.36)</td>
</tr>
<tr>
<td>SHEP61</td>
<td>4,736 systolic hypertensives; mean age of 72 years</td>
<td>Diuretic (chlorthalidone) with possible addition of β blocker (atenolol) or sympathetic nervous blocker (reserpine) vs. placebo</td>
<td>Short-CARE</td>
<td>4.5 (years)</td>
<td>Mean difference in BP between the treatment and placebo groups was 12 mm Hg systolic and 4 mm Hg diastolic; the rates of dementia incidence on placebo and active treatment were 4.2 and 3.6 cases per 1,000 patient-years (relative risk reduction: 14%; 95% CI: −26 to 54%) without significance</td>
</tr>
<tr>
<td>HYVET-COG62</td>
<td>3,336 hypertensives (SBP 160–200 and DBP &lt; 110 mm Hg); age ≥ 80</td>
<td>Diuretic (indapamide) with possible addition of ACE-I (perindopril) vs. placebo</td>
<td>MMSE</td>
<td>2.2 (years)</td>
<td>Mean difference in BP between the treatment and placebo groups was 15 mm Hg systolic and 5.9 mm Hg diastolic; the rates of dementia incidence on placebo and active treatment were 38 and 33 cases per 1,000 patient-years (hazard ratio 0.86; 95% CI: 0.67–1.09) without significance</td>
</tr>
<tr>
<td>Syst-Eur64</td>
<td>2,418 systolic hypertensives; mean age of 70 years</td>
<td>CCB (nitrendipine) with possible addition of ACE-I (enalapril), diuretic (hydrochlorothiazide), or both vs. placebo</td>
<td>MMSE</td>
<td>3.9 (years)</td>
<td>Mean difference in BP between the treatment and placebo groups was 7.0 mm Hg systolic and 3.2 mm Hg diastolic; the rates of dementia incidence on placebo and active treatment were 7.4 and 3.3 cases per 1,000 patient-years (risk reduction: 55% risk reduction; 95% CI: 24–73%) with significance</td>
</tr>
<tr>
<td>PROGRESS65</td>
<td>6,105 subjects with prior stroke or transient ischemic attack; mean age of 64 years</td>
<td>ACE-I (perindopril) with possible addition of diuretic (indapamide) vs. placebo</td>
<td>MMSE</td>
<td>3.9 (years)</td>
<td>Mean difference in BP between the treatment and placebo groups was 9.0 mm Hg systolic and 4.0 mm Hg diastolic; the rates of dementia incidence on placebo and active treatment were 7.1 and 6.3% (relative risk reduction: 12%; 95% CI: −8 to 28%) without significance; the rates of cognitive decline on placebo and active treatment were 11.0 and 9.1% (risk reduction: 19%; 95% CI: 4–32%) with significance</td>
</tr>
<tr>
<td>HOPE66</td>
<td>9,297 patients with vascular disease or diabetes plus an additional risk factor; age ≥ 55</td>
<td>ACE-I (ramipril) vs. placebo</td>
<td>—</td>
<td>4.5 (years)</td>
<td>Mean difference in BP between the treatment and placebo groups was 3.8 mm Hg systolic and 2.8 mm Hg diastolic; the rates of cognitive decline on placebo and active treatment were 0.6 and 1.1% (relative risk: 0.59; 95% CI: 0.37–0.94) with significance</td>
</tr>
<tr>
<td>SCOPE67</td>
<td>4,964 hypertensives; aged 70–89; SBP 160–170/DBP 90–99 mm Hg</td>
<td>ARB (candesartan) vs. placebo; Open-label antihypertensive drugs were added to both groups</td>
<td>MMSE</td>
<td>3.7 (years)</td>
<td>Mean difference in BP between the treatment and placebo groups was 3.2 mm Hg systolic and 1.6 mm Hg diastolic; 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); the rates of dementia incidence on placebo and active treatment were 6.8 and 6.3 cases per 1,000 patient-years without significance; the rates of cognitive decline on placebo and active treatment were 15.2 and 13.5 cases per 1,000 patient-years without significance</td>
</tr>
<tr>
<td>ProFESS68</td>
<td>20,332 subjects with ischemic stroke; mean age of 66 years</td>
<td>ARB (telmisartan) vs. placebo</td>
<td>MMSE</td>
<td>2.4 (years)</td>
<td>Mean difference in BP between the treatment and placebo groups was 3.8 mm Hg systolic and 2.0 mm Hg diastolic; the rates of cognitive decline on placebo and active treatment were 11 and 11% (relative risk: 0.95; 95% CI: 0.87–1.05) without significance</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CI, confidence interval; DBP, diastolic blood pressure; HOPE, Heart Outcomes Prevention Evaluation; HYVET-COG, Hypertension in the Very Elderly Trial Cognitive Function Assessment; MMSE, mini-mental state examination; MRC, Medical Research Council; PALT, paired associate learning test; PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; SBP, systolic blood pressure; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; Short-CARE, Short-Comprehensive Assessment and Referral Evaluation; Syst-Eur, Systolic Hypertension in Europe; TMT, Trail making test.
studies, there were significant differences in the rate of cognitive decline between active treatment group and control group. In the PROGRESS study, combination therapy with ACE-I (perindopril) plus diuretics (indapamide) (relative risk reduction: 23%; 95%CI: 0–41%) but not monotherapy with ACE-I alone (relative risk reduction: –8%; 95%CI: −48 to 21%), compared with placebo, reduced the incidence of dementia.

**Angiotensin II receptor blockers**

In the Study on Cognition and Prognosis in the Elderly (SCOPE), the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial, the impact of angiotensin II receptor blockers (ARBs) on cognitive function was evaluated in randomized controlled design. In both studies, there were no significant differences in the rate of cognitive decline or dementia between active treatment group and control group. In the PROFESS trial, several limitations of the study should be acknowledged, including the complexity of the two-by-two factorial study design, the short duration of follow-up period, the frequent discontinuation of the study drug among subjects, and the fact that patients who experienced recurrent stroke stopped antihypertensive treatments could have limited the length of exposure.

Additionally, in 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 ARB (eprosartan) based therapy on cognitive function assessed by MMSE. A total of 25,745 hypertensive patients aged at least 50 years were followed up for 6 months. SBP reduction by eprosartan had independent negative association with cognitive decline (odds ratio 0.77; 95%CI: 0.73–0.82). Fogari et al. reported that antihypertensive therapy with an ARB and diuretic (telmisartan and hydrochlorothiazide) showed the significant improvement in cognitive function compared with that using an ACE-I and diuretic (lisinopril and hydrochlorothiazide).

**Meta-analysis: Could antihypertensive therapy prevent the incidence of dementia?**

In a meta-analysis by McGuinness et al. that combined the results of the SHEP, Syst-Eur, and SCOPE trials, antihypertensive therapy reduced the risk of dementia by 11% (odds ratio 0.89; 95%CI: 0.69–1.16), but without statistical significance. On the other hand, in a meta-analysis by Peters et al. that combined the results of the SHEP, Syst-Eur, PROGRESS, and HYVET trials, antihypertensive therapy significantly reduced the risk of dementia (HR: 0.87; 95% CI: 0.76–1.00).

**Is there a class effect of antihypertensive agents on cognitive function?**

The exaggeration of the brain arteriosclerosis and cerebral artery remodeling by long-standing systolic hypertension may be associated with disrupted cerebral autoregulation and may result in decreased CBF. This mechanism may underlie in the relationship between high BP and declined cognitive function. In this point, early detection of hypertension and antihypertensive therapy has a beneficial effect.

Long-acting CCB, ACE-I, and ARB which does not decrease CBF are thought to be appropriate in BP control to prevent brain damage progression. Hatazawa et al. reported that long-term ACE-I (perindopril) therapy improved cerebral perfusion reserve in patients with previous minor stroke. In the diabetic hypertensives, Kario et al. showed that ARB (candesartan) therapy significantly improved cerebrovascular reserve in the internal carotid and middle cerebral arteries compared with the nondiabetic hypertensives, while that therapy did not improve cerebral metabolism assessed by N-acetyl aspartate in the white matter. On the other hand, in meta-analysis for actively controlled trials by Wang et al., CCBs reduced the progression of carotid intima-media thickening more than diuretics, β-blockers, or ACE-Is. The reduction in carotid intima-media thickness in the patients treated with a CCB were thought to be attributable to a functional decrease by its vasodilatory effect and not necessarily to a structural decrease in intima-media cross-sectional area.

From these points of views, CCB, ACE-I, and ARB would be suitable in controlling BP with brain protection via improvement of cerebral circulation. It would be a clinical relevant issue to compare the impact of cognitive protection among CCB, renin–angiotensin system inhibitor, and combination of these agents.

**CONCLUSION**

The recent literature confirms that brain matter damage caused by long-standing hypertensive status is associated with cognitive impairment. Accordingly, strict BP control including during sleep may have a neuroprotective effect on the brain, and thereby prevent the incidence of dementia.

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