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Antihypertensive Therapies and Cognitive Function: a Review

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Abstract Increasing life expectancy has made old age-related health problems like dementia and cognitive decline more prevalent, and these are rapidly becoming important causes of disability and poor quality of life, causing significant add-ons to health-care costs worldwide. Hypertension is the most important modifiable vascular risk factor for the development and progression of both cognitive decline and dementia. In many observational and randomized studies, antihypertensive therapies have been shown to be beneficial in slowing cognitive decline. However, due to observed discrepancies by these studies, there is a lack of consensus on the best antihypertensive strategy for the prevention or slowing of cognitive decline. It is also not clear whether the beneficial effect of antihypertensive therapy is due to the use of a specific class of agents or combination therapy. Thus, we present a comprehensive review of overall antihypertensive therapies and cognition and of the individual antihypertensive therapy classes with their specific protective mechanisms and available clinical evidence behind their effect on cognitive function.

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Introduction

As life expectancy increases, age-related health problems such as progressive dementia and cognitive decline are becoming more prevalent. The most frequent reasons for cognitive impairment are Alzheimer's disease (AD) and vascular dementia (VD), and it is very difficult to distinguish between the two-disease entities clinically. Existing evidence indicates that risk factors for cardiovascular disease increase the risk of developing both AD and VD [1]. Hypertension (HTN) is the most important modifiable vascular risk factor for the development and progression of both cognitive decline and dementia [2•]. Cognitive decline is rapidly becoming a major cause of disability worldwide and significantly contributes to a detrimental quality of life, increased disease burden, morbidity, mortality, and a resultant high health-care cost [2•]. As of year 2010, there were an estimated 35.6 million people with dementia worldwide with total estimated annual health-care cost of US $604 billion [3]. Thus, a preventive management strategy in the form of antihypertensive therapy early in midlife to prevent late-life cognitive decline is important and multiple pre-clinical and clinical studies have been done to support this practice [4]. Here, we review the relationship between various classes of antihypertensive treatment modalities and their individual effects on prevention of cognitive decline.

Blood Pressure and Cognition

The association between HTN and cerebrovascular disease is well described [5]. This association strengthens with

increasing age and duration of HTN. Although various theories have been advocated [6], the exact underlying mechanism of the development of AD and VD due to high blood pressure is unclear [7]. A recent review by Gasecki et al. suggested that it is the cerebral vascular damage in HTN that leads to cognitive deficit. The decline in cerebrovascular reserve capacity and increased vascular degenerative changes essentially leads to the development of both grey and white matter lesions such as micro-hemorrhages, micro-infarcts, and hyperdense white matter lesions [2•]. Hypertension also has unfavorable effects on cerebral vasoreactivity and loss of autoregulatory capacity, which are consistent with the effects seen in the patients with stroke [8]. The Cardiovascular Health Study showed HTN-induced impairments in mobility, cognition, and mood that are related to microvascular brain injury and white matter hyperdensities [9]. The Rotterdam Study pioneered in showing the role of risk factors for atherosclerosis in the occurrence of brain lesions and cognitive decline [10], with a clear overlap between AD and VD. Additionally, structural changes in the brain such as white matter hyperdensities from HTN and brain atrophy secondary to aging and chronic HTN are related to the risk of cognitive decline [11, 12]. Macrovascular dysfunction from HTN, such as arterial stiffness and elevated pulse pressure, has also been associated with the risk of cognitive decline [13, 14]. Researchers have also shown a relationship between the renin-angiotensin system and dementia progression [15] and brain aging [16]. Angiotensin II may be involved in the prevention of acetylcholine release [17•], an important neurotransmitter associated with memory.

Epidemiological studies have supported a close relationship between HTN and cognitive decline. In the Framingham Heart Study, in a cohort of 1702 individuals, including 88 % untreated hypertensive patients, the chronicity of HTN was inversely related to the composite score for attention and memory after correction for other cardiovascular and demographic risk factors [18]. Other long-term studies have specifically indicated midlife high blood pressure as a predictor of late-life cognitive decline [19, 20], mainly due to VD with some evidence of association with AD [21, 22]. In a Swedish longitudinal study, a strong correlation was shown between high systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the development of AD 10–15 years later [23]. A subsequent study of 1000 Swedish male patients with high DBP at age of 50 showed a reduced cognitive function at the age of 70 that was associated with high blood pressure, diabetes, and insulin resistance [24]. Recently, a longitudinal study of Japanese-American men in Hawaii also showed that after 20–26 years of follow-up, both high SBP and diastolic BP predicted AD and VD. In the same cohort, elevated midlife SBP was associated with senile plaques in both the neocortex and hippocampus and high DBP was associated with neurofibrillary tangles in the hippocampus [1].

At the other end of the blood pressure spectrum, Mahoney et al. showed that elderly (>70 years) patients with low SBP have worse executive attention scores than individuals with normal or high SBP [25]. In a longitudinal study of patients 80 years of age and above, there was an association of higher cognitive decline risk with lower SBP in the oldest old patients, which was consistent even after adjustment for frailty [26].

Antihypertensive Therapies and Cognitive Function

Unlike the clear relationship between HTN and cognitive decline, there is no clear consensus about the prevention of cognitive decline with antihypertensive therapies. Some well-designed randomized controlled trials (RCTs) have shown a positive correlation of antihypertensive therapy with the prevention or slowing of cognitive decline. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed a 19 % relative risk reduction in cognitive decline [27], a Heart Outcome Prevention Evaluation (HOPE) study showed a significant 41 % reduction in stroke-related cognitive decline [28], and a trial of HTN treatment in the elderly, the Systolic Hypertension in Europe (Syst-Eur) study showed a 50 % reduction in dementia incidence in the treatment group compared to placebo [29]. On the other hand, other RCTs have failed to show any significant prevention of cognitive decline with anti-HTN therapy. These include the Systolic Hypertension in the Elderly Program (SHEP) trial [30], the Study on Cognition and Prognosis in the Elderly (SCOPE) [31], the Hypertension in the Very Elderly Trial–Cognitive function assessment (HYVET-COG) trial [32], and a Medical Research Council (MRC) trial [33]. The Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trials of different renin-angiotensin system inhibition approaches also failed to show any clear effects on cognitive outcomes [34]. A large Cochrane review of four trials including more than 15,000 patients showed no significant difference in dementia incidence and MMSE decline with anti-HTN therapy [35].

One explanations of this discrepancy could be that most studies of anti-HTN therapies were not designed specifically to address the issue of cognition. They may have been inadequately powered for this kind of analysis, differences in antihypertensive treatment protocols and treatment agents used, heterogeneity in cognitive testing, and different inclusion criteria and follow-up durations. Most of these RCTs were done on an elderly population, and thus, long-term follow-up can be challenging with substantial loss to follow-up. For the clinical trials after the HYVET study, it was considered unethical to compare antihypertensive therapy with placebo

alone, which may require even longer follow-up to reach in any meaningful cognitive outcome in this patient population. Also, most studies were done on patients with low risk for cognitive impairment and not on the comparatively high-risk patients with baseline minimal cognitive impairment or evident white matter lesions on radiology, which could possibly have increased the unmet need for a large and more vulnerable study population.

Notwithstanding this uncertainty, it is important to evaluate whether the potential beneficial effect of antihypertensive therapy is related to the use of a specific class or classes of agents.

Anti-HTN Treatment Classes and Cognitive Function

Renin-Angiotensin-Aldosterone System Antagonists

Studies have supported the role of renin-angiotensin-aldosterone system (RAAS) in dementia progression and brain aging. Animal studies by Inaba et al. showed that reduced cerebral blood flow and increased oxidative stress from RAAS activation can lead to ischemic brain damage and cognitive decline in chimeric and transgenic RAAS-activated mice compared to wild-type mice [36, 37]. The constituents of RAAS have been identified in various organ systems including the heart, brain, kidney, and vascular system. Peripheral RAAS activation can lead to HTN-related cardiovascular and neural damage and to resultant dementia and cognitive impairment. The brain is known to contain all of the components of RAAS and will therefore modulate RAAS-mediated effects in addition to the effects of RAAS in the periphery. The blood-brain barrier (BBB) crossing ability is an essential pharmacological characteristic, which facilitates many of RAAS antagonists for their local neurocognitive effect [38].

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) is found mainly in the pulmonary circulation, but it has also been detected in the brain at the cerebral parenchyma and in the cerebral vasculature [39]. ACE inhibition decreases the deposition of amyloid β (Aβ) peptides via substance P, an activator of the neutral endopeptidase enzyme (neprilysin), which can degrade Aβ peptide in the brain [40, 41]. Additionally, inhibition of ACE activity in the brain also enhances the release of acetylcholine from neurons. ACE inhibitors (ACE-Is) can also reduce neuronal damage through an anti-oxidative mechanism [42]. In patients with AD, the ACE is overexpressed in the hippocampus, frontal cortex, and caudate nucleus [43], which can explain the beneficial effect of ACE-I in this patient population.

The early, small, randomized HOPE study showed that long-term adequate blood pressure control by either ACE-I or diuretics may reverse cognitive impairment associated with HTN [44]. Subsequently, the larger RCT Syst-Eur trial demonstrated that the long-term anti-HTN therapy with an ACE-I (enalapril maleate) in combination with a dihydropyridine (DHP) calcium channel blocker (CCB) (nitrendipine) reduced the risk of dementia [29]. The PROGRESS study showed that treating the patients with cerebrovascular disease with perindopril, with the possible addition of indapamide can reduce the risks of dementia and cognitive decline associated with recurrent stroke [27]. This supports the idea that patients with or without existing cerebrovascular disease can benefit from ACE-I therapy to reduce the risk of dementia and cognitive decline.

A randomized study by Ohrui et al. suggested that ACE-Is with a BBB penetrating ability (perindopril, captopril) could slow the rate of cognitive decline in mild to moderate AD patients better than non-brain-penetrating ACE-Is or CCBs [45].

Angiotensin II Receptor Blockers

Angiotensin (Ang) II mainly stimulates Ang II type 1 (AT-1) receptors in the brain causing local cellular proliferation, inflammation, and vasoconstriction, whereas stimulation of AT-2 brain receptors produces vasodilation and other neuroprotective effects [46]. Thus, angiotensin II receptor blockers (ARBs) that not only block the AT-1 receptor but also allow Ang II access to the neuroprotective AT-2 receptor [6]. AT-1 receptor blockade may also induce metabolic degradation of amyloid β deposits in the brain, which are pathognomonic for AD [47]. According to the Dementia Research Group Study, ARBs may also facilitate acetylcholine release and thus inhibit acetylcholine-specific inflammatory pathways in AD [17•].

In the randomized SCOPE study, a reduction in non-fatal stroke was observed in the candesartan-based treatment group compared to placebo while maintaining cognitive function [31]. Studies done in elderly hypertensive patients by Fogari et al. showed an improvement in episodic memory with valsartan compared to enalapril [48] and an improvement in the components of cognitive function (memory, visuospatial abilities) with telmisartan/hydrochlorothiazide compared to a lisinopril/hydrochlorothiazide combination [49]. A large prospective study of predominantly male population with cardiovascular disease showed that ARBs (candesartan, irbesartan, losartan, valsartan) significantly reduced the incidence and progression of AD and dementia and were superior to ACE-Is and other cardiovascular drugs [50]. A recent network meta-analysis showed ARBs with the strongest benefit versus placebo in overall cognition and greater effectiveness against β-blockers, diuretics, and ACE-Is in graded rank. This finding

was without any significant difference in BP amongst the studied drug classes [51•].

Aldosterone Antagonists

Mineralocorticoid receptors are present in abundance in the hippocampus, which is known to be involved in overall cognitive function. It has been suggested that a lower serum potassium concentration contributes to cognitive decline by the possible actions of vasoconstriction, inflammation, oxidative stress, and platelet aggregation [52]. The incidence of cerebrovascular disease was shown to be significantly higher in patients with primary aldosteronism than in an essential HTN group [53]. Additionally, high plasma aldosterone levels were shown to be directly associated with cognitive dysfunction and, thus, aldosterone antagonists, spironolactone and eplerenone, are shown to be protective against cognitive impairment in hypertensive patients [54]. In the Cache County Study, incidence of AD was lower in hypertensive patients treated with any antihypertensive medication but with the greatest benefit with potassium-sparing diuretics [55]. Recently, the randomized Ginkgo Evaluation of Memory Study (GEMS) showed improved verbal learning and memory function with potassium-sparing diuretic use compared with no anti-HTN or even with the use of other anti-HTN therapies (ACE-Is or ARBs) in non-demented elderly patients [56].

Calcium Channel Blockers

According to the position paper of the American Society of Hypertension, disturbed intracellular calcium homeostasis may have an effect on cognitive decline [6]. The aged brain losses its capability of intracellular calcium degradation [29], which can potentially lead to cellular damage and death and subsequent cognitive impairment [57]. The BBB crossing ability of lipophilic CCBs allows inhibition of neuronal calcium influx and, thus, possibly provides benefit against cognitive decline [58]. Nimodipine has been shown to improve cognitive function in patients with VD; nimodipine has also been shown to improve memory in post-infarct patients, if treated for 3 months starting 7–14 days after cerebral infarction [59]. The Scandinavian Multi-Infarct Dementia Trial suggested a favorable effect of nimodipine on neuropsychological testing in a post hoc analysis of subgroups of patients with subcortical VD [60]. The double-blind randomized Syst-Eur trial of elderly hypertensive patients showed that treatment with nitrendipine with an add-on of enalapril maleate or hydrochlorothiazide protected against dementia [29]. The Leiden 85-plus study evaluated and confirmed that the dementia-preventive action of calcium antagonists is a BP-independent calcium channel inhibition action [58].

Beta-Blockers

The exact mechanism of any beneficial effect of beta-blocker (βB) on cognition is unclear. It has been associated that any suggested beneficial effect would be related to blockade of cerebral β-receptors, so that those βBs which cross the BBB would be expected to be most effective at reducing cognitive decline [6]. In an animal study of AD, carvedilol was shown to restore basal synaptic transmission, improve neuronal plasticity, reduce neuronal hyperexcitability [61], and diminish β-amyloid content in the brain and, thus, reduction in cognitive decline [62]. Another senescence-accelerated mouse study showed reduced β-amyloid and tau pathologies and an improved cognitive function with the use of propranolol [63].

In clinical studies, βB produced varied results for cognitive function. A small clinical study by Madden et al. showed a slight improvement in short-term memory with βB (propranolol, atenolol), which was not different from placebo [64]. The cognitive sub-study of the MRC trial of HTN in older adults showed no influence of βB on cognitive function compared to placebo when used as a treatment of moderate HTN [33]. A study on very elderly patients with HTN by Fogari et al. showed a neutral effect of atenolol on cognitive function [65]. However, in the recent randomized GEMS trial, βB was shown to have reduced risk of AD in patients with normal cognition at baseline, although the effect was smaller compared to other antihypertensive classes like ACE-Is, ARBs, and diuretics [66•]. The community-based Honolulu-Asia Aging Study (HAAS) of elderly hypertensive Japanese-American men showed a reduced risk of cognitive impairment with use of βB [67•].

Diuretics

There is a lack of any clear mechanistic explanation for the effect of diuretics on cognition, including the potassium-sparing diuretics as described in the above section. Diuretics have been studied in cognition trials but mostly as an add-on therapy rather than as a principal study drug. The randomized HOPE study concluded that optimum BP control with a diuretic (bendrofluazide) or ACE-I (captopril) may reverse cognitive impairment in elderly patients with pre-existing cognitive impairment associated with HTN [44]. Conversely, the MRC trial of HTN in older adults did not show any cognitive benefit with diuretics in treatment of moderate HTN [33]. The SHEP trial failed to find any significant difference in the incidence of cognitive decline between participants receiving active treatment (low-dose diuretic and/or BB) and those receiving placebo. This finding has been challenged on the basis of a claim of missing data and loss to follow-up on outcome assessment [68]. The addition of a diuretic hydrochlorothiazide to long-term anti-HTN therapy with a DHP-CCB (nitrendipine) and/or an ACE-I (enalapril maleate) reduced

dementia risk in the Syst-Eur trial [29]. Also, in the PROGRESS study, indapamide in combination with perindopril showed higher risk reduction for dementia and cognitive decline associated with recurrent stroke compared to perindopril alone or placebo group [27]. Active treatment was associated with a reduced risk of dementia and cognitive decline associated with recurrent stroke. A randomized trial by Fogari et al. also showed an additive effect of HCTZ to telmisartan or lisinopril in better BP reduction and improvement in cognitive functions such as episodic memory and visuospatial abilities [49]. Interestingly, HYVET-COG study showed no significant reduction in dementia incidence by antihypertensive treatment with indapamide and/or perindopril compared to placebo, but when the study data were applied in a meta-analysis with other placebo-controlled trials of antihypertensive treatment, the combined risk ratio favored diuretic-based treatment in the reduction of dementia [32]. Recently, GEMS showed a reduced risk of AD in patients with normal cognition and also with mild cognitive impairment [66•]. In patients with ischemic stroke without atrial fibrillation, antihypertensive therapy with diuretic alone or in combination with ACE-I had a significant secondary preventive effect on cognitive decline [69•].

Conclusion

Multiple observational and randomized studies have been reported in the field of antihypertensive therapy and cognition without any consensus and a resultant lack of any clear recommendation to support the use of any one class of antihypertensive agent versus another in the prevention of cognitive decline. Many of the RCTs, which have addressed this question, have major methodological issues. These were mainly sub-studies or post hoc analysis for cognitive assessment using heterogeneous drug classes, under powered, too short of duration, and using non-uniform complex psychometric testing, which all mitigate against any credible meta-analysis in this field. It would seem that each therapy has limited beneficial effect, or a neutral effect, on cognition, but without any harmful effects. It is also noteworthy that various studies have used different cognition assessment strategies without any harmony. The mechanistic explanation of any beneficial effect of any anti-HTN therapies on cognitive function is unclear but could be either an effect of BP lowering or a direct neuroprotective effect of the drug. Drug property of crossing a BBB has been seen as a common factor in such latter effect, but this requires dedicated study for the explanation.

In a recent network meta-analysis of hypertensive patients without any prior cerebrovascular disorder, ARBs were better than placebo, βB, diuretics, and ACE-Is in rank order. Also, DHP-CCBs were shown to be beneficial in the Syst-Eur trial, independent of the antihypertensive effect, and supported a class-specific effect on cognition. Upcoming the Systolic blood PRessure Intervention Trial (SPRINT) is a multicenter RCT evaluating the impact of optimal SBP control (<140 versus <120 mmHg) on various clinical outcomes including cognitive function [70•]. In the two dedicated SPRINT substudies, Systolic Blood Pressure Intervention Trial: Memory and cognition IN Decreased hypertension (SPRINT MIND) and Systolic Blood Pressure Intervention Trial: Memory and cognition IN Decreased hypertension Magnetic Resonance Imaging (SPRINT MIND MRI) investigators have used extensive cognitive assessment techniques like screening battery, the Functional Assessment Questionnaire (FAQ), an extended cognitive assessment battery using the Montreal Cognitive Assessment (MoCA), and additional structural brain imaging using MRI. Additionally, different anti-HTN medications used in this study will help identify any particular beneficial or detrimental drug effect on cognition.

If any conclusion is to be drawn at this point, it is that the available evidence supports a preference for ARBs, ACE-Is, and CCBs for the prevention of cognitive decline in the patients with HTN. It also becomes apparent that combination therapies are more protective than monotherapy regardless of drug class, due to a possible additive systemic or neuronal effect. There is clearly a need for additional well-designed RCTs comparing various antihypertensive strategies to quantify cognitive benefit in the middle-aged to elderly patient population with and without baseline cognitive impairment, which is sufficiently powered, of sufficient duration, and using standardized psychometric tests. Given the pharmacoeconomics of the drug testing, this is unlikely to be underwritten by the pharmaceutical industry, so it will be left to the other funding agencies to fill this very real need.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Kherada, Dr. Heimowitz, and Dr. Rosendorff declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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