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HYPERTENSION AND THE BRAIN (I NASRALLAH, SECTION EDITOR)

Effects of Hypertension on Alzheimer's Disease and Related Disorders

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Abstract

Purpose of Review To review the pathophysiology of hypertension in Alzheimer's disease and related dementias and explore the current landscape of clinical trials involving treatment of hypertension to improve cognition.

Recent Findings Hypertension is increasingly recognized as a contributor to cognitive impairment. Clinical trials that explore blood pressure reductions with cognitive outcomes have been promising. Various antihypertensives have been evaluated in clinical trials, with growing interest in those agents that impact the renin–angiotensin–aldosterone system due to its own association with cognitive impairment. No antihypertensive agent has been found to be superior to others in reducing cognitive impairment risk or conferring neuroprotective benefits. In this review, the pathophysiology of and clinical trial data involving hypertension and dementia will be explored.

Summary Hypertension is a significant risk factor for the development of neurodegenerative dementias, and clinical trials have been overall favorable in improving cognition by reductions in blood pressure using antihypertensive agents.

Keywords Hypertension · Dementia · Alzheimer's disease · Cognitive function

Introduction

Hypertension (HTN) is one of the commonest diseases known to man, affecting as many as one billion adults. The effects of hypertension on the nervous system are varied and include both direct and indirect effects. Direct effects include the relationship of neuronal and neuronal network function modulated by the effects of hypertension on cerebral vasculature. Indirect effects may be more common and include stroke both thrombotic and embolic through hypertensive effects on heart and both large and small cerebrovascular vessels. Hypertension affects other major organs particularly the kidneys and the eyes; renal insufficiency is well-known to cause cognitive decline in proportion to glomerular filtration rate (GFR) decline, and the visual system can be considered an extension of the central nervous system insofar as the retina is composed of neural tissue.

Dementia is the term given to the constellation of memory loss and other cognitive functions, including executive, visuospatial, language, and behavioral function sufficient to cause a significant loss of function in activities of daily living (ADL). More mild cognitive loss, both subjective cognitive impairment (SCI) and mild cognitive impairment (MCI) with either chronic or acute onset has been recognized to be quite common in older populations.

Alzheimer's disease (AD) is the commonest form of adult dementia with a strong risk with advancing age, and known genetic influences. Alzheimer's disease–related disorders (ADRD) include a number of conditions that have similar trajectories, overlapping pathology and common cognitive symptoms. The major components of ADRD include vascular cognitive impairment (VCI)/vascular dementia (VaD) with stroke or extensive white matter pathology, Parkinson's disease (PD) and other Parkinsonian disorders, and the diverse syndrome known as Frontotemporal dementia. The latter includes syndromes such as Pick's disease, Primary Progressive Aphasia, progressive supranuclear palsy, corticobasal degeneration, and motor neuron disease. In this review, we explore current knowledge about the relationship of HTN and these neurological disorders at the molecular, clinical, and epidemiological levels.

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Epidemiology of Hypertension

Hypertension affects more than 1 billion people worldwide and is a common risk factor for both cardiovascular disease risk and cognitive impairment, contributing to 4.5% of the total global disease burden [1]. In the USA, it is estimated that 45% of adults have hypertension or are taking medications for this; however, only 24% of these Americans will have their hypertension under control [2]. In regard to sex, hypertension is more common in men than women. Racial differences are also seen with hypertension, with non-Hispanic black adults having the highest prevalence (54%) compared to non-Hispanic whites (46%), non-Hispanic Asians (39%), and Hispanic adults (36%). Hypertension is also more prevalent with age, increasing from 60.1% in adults 45–64 years to 77% in those older than 65 years of age, based on the 2015–2018 NHANES data [3]. Revised high BP guidelines were created in 2017 through the ACC/AHA [4]. Based on the latest guidelines, stage 1 HTN was classified as SBP: 130–139 or DBP: 80–89; stage II hypertension: SBP ≥ 140 or DBP at least 90 mmHg. Normal BP is considered SBP < 120 and DBP < 80. This effort from the ACC/AHA may lead to better outcomes through more intensive HTN treatment but it is unclear how these may improve cognitive outcomes in a community setting.

Hypertension and Cognitive Impairment

Longitudinal observational studies have been conducted to assess the risk of cognitive impairment in those with HTN. The Honolulu-Asia Aging Study included 3703 Japanese men over ≥ 65 years of age, recording their blood pressure between ages 45–68, and following them for 25 years [5]. An increased risk of both AD and VCI was noted in this population at high blood pressures in midlife. The ARIC study (13,476 subjects with a 20 year follow-up) also showed that deficits in global composite cognitive function, verbal fluency, and cognitive speed were greater in persons with higher baseline HTN [6]. The Swedish Gothenburg H-70 study, found that subjects who developed dementia at ages 79–85 had higher systolic and diastolic blood pressures recorded age 70 than those who did not develop dementia (i.e. SBP means 178 vs. 164 mmHg; DBP means 101 vs. 92 mmHg) [7].

A meta-analysis performed by Ou et al. looked at 209 prospective studies to further characterize the relationship of blood pressure and cognition [8••]. The effect exerted by hypertension on cognitive impairment appears to be based, in part, on the age at which hypertension is observed: the risk for cognitive impairment after age 65 was higher in adults who had elevated blood pressure in the midlife age range (40–64), with hazard ratios ranging from 1.19 to 1.55. SBP ≥ 140 and DBP ≥ 90 mmHg were threshold BP parameters that showed an increased risk for dementia and AD. DBP ≥ 90 in particular incurred a 51% risk of AD. A nonlinear dose–response curve was supported, with SBP > 130 mmHg, the risk of dementia increased. Lower DBP (< 65 mmHg) was associated with a RR of 1.7 (95% CI 1.1–2.4) for developing AD, whereas higher DBP readings (i.e. ≥ 90 mmHg) were not.

As to late-life HTN, the evidence is more neutral regarding the effects of HTN on cognition, with a RR of 1.02 (95% CI, 0.94–1.10], although there was a modest associated with dementia risk in the black population compared to whites, Asians, and mixed populations that were assessed [8••]. Interestingly, the DBP in the late-life population exhibited a U-shaped curve, wherein the DBP range of ≥ 90 mmHg showed a 23% risk reduction in AD. This appears consistent with a previous longitudinal analysis, the Kungsholmen Project, wherein 1270 subjects were followed for 6 years [9]. In this cohort, higher SBP (> 180 mmHg) conferred a relative risk of 1.5 for AD (95% CI 1.0–2.3), whereas DBP > 90 mmHg did not. In fact, the Lower DBP (< 65 mmHg) was associated with a RR of 1.7 (95% CI 1.1–2.4). for developing AD, whereas higher DBP readings (i.e. ≥ 90 mmHg) were not.

Vascular risk factors also seem to predict which patients with mild cognitive impairment (MCI) convert to AD. Hypertension also seems to affect certain cognitive domains more so than what is suggested by chance, including executive function, cognitive speed, abstraction [10].

A recent longitudinal study by de Menezes et al. followed 7063 participants with a mean age of 58.9 years over a period of 3.8 years [11••]. The participants' BP was checked at baseline. Two visits were conducted, wherein cognitive testing with standardized memory, verbal fluency, trail B, and global cognitive scoring were performed. What they found is that participants with either prehypertension (i.e. SBP: 121–139 and DBP: 81–89) or HTN at the baseline assessment were associated with decreased cognitive performance: prehypertension showing decline in fluency and hypertension in memory, and both associated with decreased global cognitive scores. This paper, along with a few others, have considered the role of the prehypertensive stage and its impact on cognition.

Non-AD Dementias and High BP

The majority of the literature exploring the role of elevated BP and dementia is focused on AD or composite dementias. For frontotemporal dementia (FTD), Golimstock et al. noted an increased risk for FTD in patients with diabetes mellitus compared to those without (39% vs. 22.6%) in their population of 100 FTD participants and 200 age-matched controls [12]. Other cardiovascular disease risk factors were found to have no statistically significant difference. More research is required to assess the relationship

between cardiovascular disease risk factors and FTD. The picture is also unclear for the relationship between PD and HTN. The use of certain AHMs, such as dihydropyridine CCBs, appears to reduce the risk of developing PD [13]. Other studies have shown that the presence of vascular risk factors in PD patients may worsen cognitive and motoric function [14, 15••].

Hypertensive Arteriopathy in the CNS and Cognition

Hypertension itself is most strongly linked with the development of cerebrovascular disease due to its impact on the intracranial vasculature. Possible mechanisms for the effects of high blood pressure in the CNS include alterations in the microvasculature milieu, endothelial dysfunction, reduced cerebral blood flow, and regional hypoxia [16]. A spectrum of pathologies from hypertensive arteriopathy is known, many of which may be seen with conventional magnetic resonance imaging (MRI) [17•]. These include cerebral small vessel disease, deep cerebral microbleeds, white matter hyperintensities, basal ganglia perivascular spaces, lacunar strokes, and cerebral amyloid angiopathy [18]. These pathologies have been associated with cognitive impairment. For example, the presence of white matter hyperintensities noted on T2-weighted MR imaging have been associated with dementia as well as cognitive deficits in executive function and processing speed [18]. In addition to increasing the risk of cognitive impairment, some of these sequelae of hypertensive arteriopathy alter the course of dementia. In the Nun study, subjects who had lacunar strokes in addition to Alzheimer pathology had an increased risk for the development of dementia [19] and form the phenotypic descriptors under the umbrella term of vascular cognitive impairment (VCI). VCI may refer to a form of Mild Cognitive Impairment due to vascular causes, but extensive white matter changes are incorporated into the NINDS-AIREN criteria for vascular dementia, although the specific method for grading and making clinical decisions to call it vascular dementia (rather than other etiologies is often left to clinician's discretion in order to account for the degree of heterogeneity with cognitive changes associated with cerebrovascular diseases [20, 21].

Hypertension, Cerebrovascular Disease, and Dementia: Pathological Insights

Alzheimer's disease is the commonest dementing illness, classically manifesting as a progressive amnestic disorder, particularly with episodic memory [22]. There is considerable heterogeneity of the presentation of Alzheimer's disease, as multiple variants exist. The pathological hallmarks of Alzheimer's disease are extracellular plaques composed primarily of beta-amyloid, and intracellular neurofibrillary tangles due to hyperphosphorylated tau protein aggregates. Research has shown that vascular risk factors play a significant role in Alzheimer's disease risk and development, and that dementias in general may have more than one underlying neuropathology. A populated-based autopsy study conducted in Olmsted County, Minnesota, showed a 25% contribution of vascular disease amongst dementia cases [23]. Another study, involving a community-based pathological cohort, showed that vascular disease contributed to up to 54% of dementia cases at autopsy [24].

Multiple mechanisms have been proposed that attempt to unite the co-occurrence of AD with cerebrovascular pathology. Cerebral ischemia can lead to metabolic abnormalities in the parenchyma, resulting in increased activity of beta-secretase 1, which is responsible for cleaving amyloid precursor protein into beta-amyloid, driving amyloid plaque development [25]. Breakdown of the blood–brain barrier through chronic hypertension can also decrease the clearance of beta-amyloid [26•] Biomarker studies have also noted an association with AD and CVD, with increased AB accumulation in patients with greater arterial stiffness, white hyperintensities, and microbleeds [26•, 27].

High blood pressure has also been linked to disruption of the blood–brain barrier, as the increased intraluminal pressure leads to increased reactive oxygen species formation and weakening of the vessel walls. The breakdown of the blood–brain barrier permits access of the contents in the plasma into the CNS, which leads to a pro-inflammatory state [28]. Microglial activation and neuroinflammation in the CNS are thought to play an important role in AD pathology, as animal models have shown AD-like pathologies within this neuroinflammatory milieu [26•, 27–30].

A review by Nasrabady et al. studied the evidence for white matter abnormalities in AD with a focus on myelin and oligodendrocytes, and discussed the relationship between white matter changes and the hallmarks of Alzheimer's disease. Several mechanisms were reviewed like ischemia, oxidative stress, excitotoxicity, iron overload, beta-amyloid toxicity, and tauopathy which could affect oligodendrocytes. The review concludes that white matter changes, and particularly myelin and oligodendrocytes, could play an important role in the mechanistic underpinnings of AD pathology and this could be targeted in the potential future treatments of AD [31].

Cerebral autoregulation refers to myogenic, autonomic, and metabolic mechanisms that maintain adequate blood perfusion to the brain despite changes in blood pressure [32, 33]. Although a single study of sporadic AD patients showed impaired cerebrovascular autoregulation, most studies have

shown that cerebrovascular autoregulation is unaffected in AD patients [34–37]. However, it is established that having either low blood pressure (hypotension) or high blood pressure (hypertension) increases the likelihood of developing dementia and AD [38–40]. In particular, elevated systolic blood pressure (BP) is a major vascular risk factor for developing AD and is also associated with cerebrovascular disease, including stroke and cerebral infarcts [41–43]. Accordingly, hypertension-induced vascular changes, such as small vascular lesions and BBB damage, possibly contribute to the development of chronic cerebral hypoperfusion (CCH) and cognitive deficits [44, 45]. A neuroimaging study showed AD patients with hypertension had worse cognitive function and reduced hippocampal metabolism compared to normotensive AD patients. Interestingly, no differences in beta-amyloid were observed between these AD patients [46]. Another study showed hypertension in AD patients accelerated the rate of cognitive decline only in AD patients under the age of 65 [47]. A study in older patients (aged 71–85) with moderate AD found decreases in BP as the disease and cognition worsen, whereas others showed a decrease in BP years before cognitive decline [48, 49]. Although a comprehensive report concluded that reducing BP in hypertensive people does not help prevent cognitive decline or the development of dementia, methodological variation of these studies resulted in self-reported problems with the analyses performed [50].

The discordant results of these studies may be attributed to the differential effect that CCH or BBB deterioration would have on BP in subjects, thereby skewing the selection criteria. For example, someone who was hypertensive prior to AD diagnosis could have developed a cardiovascular abnormality, such as CCH, which would result in lower BP readings and a subsequent "normotensive" categorization during the study design. Therefore, prospective, longitudinal studies are warranted to examine the effect of lowering BP on the development of dementia or AD that carefully factor in differences in BP and presence/absence of vascular irregularities, such as CCH. One study following MCI patients for 6 years found that higher plasma levels of atrial natriuretic peptide, involved in diuresis and lowering BP, were associated with conversion from MCI to dementia or probable AD. However, MCI patients with increased atrial natriuretic peptide levels that received antihypertensive treatment had a lower likelihood of converting to probable AD [51]. It is thought that elevated atrial natriuretic peptide is indicative of disturbed vascular function, which could be used as an early biomarker to determine the optimal therapeutic treatment window in MCI patients at risk for converting to AD. Overall, we know that hypertension is implicated with the development of dementia and AD, but the effect of using antihypertensive medications to halt the progression from early cognitive symptoms into AD is still inconclusive. In addition to continuing studies to test the effectiveness of antihypertensive treatments, we must identify and study alternative targets related to hypertension-induced effects, such as damaged blood vessels from microinfarcts.

Biomarkers of Dementia and Hypertension

Beta-Amyloid and Blood Pressure

The full relationship between hypertension and beta-amyloid burden and other variables such as clinical diagnosis of Alzheimer's disease and Apolipoprotein E (APOE) status are quite complex [52, 53]; this field is also being revisited since advances in neuroimaging such as amyloid PET and now tau PET are enabling greater precision of diagnosis across clinical populations in line with new staging framework for AD [53, 54].

At a simple level of resolution, it is known that hypertension doubles the risk of AD [55]. The complexity of these overlapping relationships is highlighted by the findings from a clinical study of 259 normal controls and 79 clinical patients with AD conducted by Jeon et al. [52]. In one of their analyses of APOE e4 carriers vs APOE e4 non carriers, hypertensive ApoE e4 carriers had an increased frequency of beta-amyloid deposition and cortical thinning, common structural findings in AD [52]. The same findings were not noted in hypertensive APOE e4 non-carriers. Clark et al. showed that persons with a combination of hypertension and increased beta-amyloid burden had an accelerated cognitive decline when compared to either of the risk factors alone [56]. Yun et al. showed that persons with obstructive sleep apnea (a known risk factor for elevated BP) with increased beta-amyloid deposition have an accelerated progressive cognitive decline course when compared to controls [57].

An interesting finding in Gottesman et al. study was that vascular risk factors in older persons were not associated with increased beta-amyloid burden [55]. Faraco and colleagues showed that hypertension increased beta secretase activity leading to increased beta-amyloid 1–42 and increased beta-amyloid 42/40 ratio [58]. Ashby et al. were able to demonstrate postmortem that hypertensive persons had greater beta-amyloid burden compared to normotensive subjects [59]. Another interesting finding is that treated hypertensive persons may have increased beta-amyloid burden compared to untreated hypertensives [59, 60]. Perrotta et al. also noted that beta-amyloid deposition led to neurotoxicity and neuronal death and that hypertension accelerates the deposition of microvascular beta-amyloid [60].

The relationship between hypertension and beta-amyloid deposition may also be reciprocal. Hypertension is a risk factor for AD, and hypertension has been noted with increased beta-amyloid burden, which in turn is associated with the

development of AD. Beta-amyloid often accumulates in the perivascular spaces leading the disruption in the blood brain barrier causing a dysregulation of brain homeostasis [61, 62] The damaged blood–brain barrier may affect cholinergic neurons whose terminals directly interact with foot processes of the astrocytes, which are an essential part of the blood brain barrier.

Hypertension and Tau

The relationship between intracellular tau tangles and hypertension is also unclear. Kester et al. [63] showed that hypertension in the setting of homozygous ApoE e4 individuals was associated with higher CSF phosphorylated tau (p-tau)181 species (p-tau181) and total tau levels when compare to hypertensive people who either ApoE e4 noncarriers or heterozygous for ApoE e4 [63]. They concluded that hypertension has a detrimental effect on AD dementia pathology.

Glodzik et al. reviewed the effect of blood pressure in cognitively intact elderly people with and without hypertension. They noted that only people with hypertension who had an overall reduction in Mean Arterial Pressure (MAP) showed decreased memory and increased CSF p-tau181 levels. In the entire study group ($N=77$ followed for approximately 2 years), they noted an elevation in CSF p-tau181 and reduction in hippocampal volume, [64]. Their overall conclusion was that the hypertensive group may be sensitive to blood pressure reductions.

Petrovitch et al. looked at the relation between midlife hypertension and pathologies associated with dementia in the Honolulu-Asia aging study [65]. They found that systolic blood pressure over > 160 mm Hg was associated with increased neuritic plaques and neurofibrillary plaques deposition throughout the cortices and hippocampus and lower total brain volume. In that study, diastolic blood pressure > greater 95 mmHg was associated with increased deposition of neurofibrillary tangles in the hippocampus [65]. The findings in that study were limited because of the lack of female participants.

Moonga et al. [46] reviewed AD patients with and without hypertension. They found that persons with AD and hypertension when compared to AD persons without hypertension were more cognitively impaired, had greater burden of neuropsychiatric symptoms, and greater hypometabolism in the hippocampus bilaterally. Interestingly in their findings they noted that hypertension did not affect the numbers of neuritic plaques and neurofibrillary tangles [46].

Neurofilament Light

Neurofilament light (NfL) is an emerging marker of axonal degeneration. A recent study by Walsh et al. investigated the relationship between white matter hyperintensities (WMHs) and plasma NfL in a large elderly cohort with, and without, cognitive impairment [66]. The Alzheimer's Disease Neuroimaging Initiative (ADNI) data was used and included 163 controls, 103 participants with a significant memory concern, 279 with early mild cognitive impairment (EMCI), 152 with late mild cognitive impairment (LMCI), and 130 with Alzheimer's disease, with 3 T MRI and plasma NfL data. Multiple linear regression models examined the relationship between WMHs and NfL, with and without age adjustment. Additional covariates including smoking status, history of hypertension, history of diabetes, and BMI were added to examine the effect of vascular risk. Results showed increases of between 20 and 41% in WMH volume per 1SD increase in NfL in significant memory concern, early mild cognitive impairment, late mild cognitive impairment, and Alzheimer's disease groups ($p<0.02$). Marked attenuation of the positive associations between WMHs and NfL was seen after age adjustment, suggesting that a significant proportion of the association between NfL and WMHs is age-related. No effect of vascular risk was observed. These results are supportive of a link between WMH and axonal degeneration in early to late disease stages, in an age-dependent, but vascular risk-independent manner [66].

Hou et al. studied if common neurologic biomarkers were different in ESRD patients (defined of ESRD was receiving maintenance hemodialysis for > 3 months) and to differentiate if the specific biomarkers could correlate with specific correctable risk factors [67]. In total, 67 participants aged > 45 years were enrolled. The cognitive impairment was defined as a Mini-Mental State Examination score of < 24. The participants were divided into groups for ESRD with and without cognitive impairment. The blood-based biomarkers (tau protein, Aβ1/40, Aβ1/42, and NfL) were analyzed through immunomagnetic reduction assay. Other biochemical and hematologic data were obtained simultaneously. The study enrolled 43 patients with ESRD who did not have cognitive impairment and 24 patients with ESRD who had cognitive impairment [Mini-Mental State Examination (MMSE): 27.60 ± 1.80 vs. 16.84 ± 6.40, $p<0.05$]. Among the blood-based biomarkers, NfL was marginally higher in the ESRD with cognitive impairment group than in the ESRD without cognitive impairment group (10.41 ± 3.26 vs. 8.74 ± 2.81 pg/mL, $p=0.037$). The concentrations of tau protein, amyloid β 1/42, and amyloid β 1/40 ($p=0.504$, 0.393, and 0.952, respectively) were similar between the two groups. The area under the curve of NfL to distinguish cognitively impaired and unimpaired ESRD patients was 0.687 (95% confidence interval: 0.548–0.825, $p=0.034$). There was no correlation between the concentration of NfL and MMSE among the total population ($r=-0.153$, $p=0.277$), patients with ($r=0.137$, $p=0.583$), or without cognitive impairment ($r=0.155$, $p=0.333$). Results revealed that

patients with ESRD with cognitive impairment had marginally higher plasma NfL concentrations. NfL concentration was not correlated with the biochemical parameters, total MMSE among total population, or individual groups with or without cognitive impairment [67].

Clinical Trials and Dementia Prevention

The relationship between blood pressure control and improving cognition or more commonly reducing the risk of cognitive decline is complex. Studies looking at this question have had conflicting results. Some studies such as ACCORD, which measured hypertension control in persons with diabetes, did not show a reduction in dementia risk but did show a reduction in slowing white matter lesion progression, whereas SPRINT, in which blood pressure was very tightly controlled at or below 120/80 mmHg versus 140/90 mm Hg noted a reduction in the risk of developing cognitive decline [68–71, 72••]. The role of hypertension is further muddled in cognitive decline when the age of the person is taken into account. In some studies, it is noted that in persons over the age of 90, hypertension is associated with reductions in cognitive decline [73, 74].

The Study on Cognition and Prognosis in the Elderly (SCOPE)

SCOPE was a prospective, double-blind, randomized parallel-group study conducted in 1997–2002 [75]. The study showed that a slightly more effective blood pressure reduction during candesartan-based therapy in elderly hypertensive patients was associated with a modest, statistically non-significant, reduction in major cardiovascular events and with a marked reduction in non-fatal stroke compared with control therapy. The presence of substantial blood pressure reductions in both treatment groups was associated with a well-maintained cognitive function [75].

Systolic Hypertension in Europe Study

The Systolic Hypertension in Europe (Syst-Eur) was one of the first double-blind studies followed by an open-label study that aimed at dementia prevention. The study was terminated early in 1997 because the primary outcome of stroke showed a significant reduction with BP control. Syst-Eur showed a reduction in the incidence of dementia by 50% from 7.7 to 3.8 cases/1000 subjects/year, but there were only 32 incident cases overall, limiting the result's interpretation. In a follow-up study, the incidence of dementia cases was increased to 64 cases with 41 persons having Alzheimer's disease (AD). The study concluded that for 1000 patients treated with nitrendipine, an additional 20 cases of dementia were prevented [76].

The limitations of the Syst-Eur study include the use of a single agent nitrendipine which is not available in the USA, and limited duration of the study. The absolute number of cases was small, especially in the relatively short double-blind phase, and it has been suggested that the practical benefits were therefore of limited value [76]. However, as proof of concept, Syst-Eur remains an important landmark, and some of the experiences from that study have been repeated in later studies, such as early termination of both HYVET and SPRINT.

Hypertension in the Very Elderly Trial (HYVET) Study

The HYVET study enrolled 4761 subjects throughout Europe, China, Tunisia, Southeast Asia, and Australia, over age 80 years. Three thousand three hundred thirty-six subjects of 3781 randomized had at least two visits and a mean follow-up of 2.2 years. The main study was again terminated early because interim analysis showed benefit with lower BP with reductions in mortality, stroke, and heart failure. The study itself did not show a significant dementia risk reduction based on 263 cases of incident dementia. The results were suggestive of an emerging effect, but the short follow-up precluded it from reaching statistical significance. However, when data were combined in a meta-analysis of other placebo-controlled studies, the combined risk ratio favored treatment over placebo (HR = 0.87, 95% CI 0.76–1.0 and $p = 0.045$) [77].

Systolic Pressure Reduction Intervention Trial (SPRINT)

SPRINT was designed to compare the effectiveness of two different blood pressure targets, namely 120/80 mmHg (intensive treatment) *versus* 140/90 mmHg (standard treatment) [71, 72••]. The study subjects were aged 50 years and above and known to have increased Framingham cardiovascular risk scores, or subclinical risk with chronic kidney disease stage 3, defined as a glomerular filtration rate 40 to 60 mL/min/1.73 m2. The study enrolled 9361 subjects and included an expanded cohort > 75 years in age. SPRINT-MIND occurred in several phases and the subjects were followed for a median of 3.3 years The main study was stopped prematurely in 2015 after positive results of analyses showed reductions in the composite endpoint of cardiovascular events and mortality favoring intensive BP control [71]. The primary pre-specified outcome was a reduction in incident all-cause dementia. Dementia occurred in 149 subjects and was not statistically significant between groups. Analyzing mild cognitive impairment and dementia showed significant differences favoring intensive BP control (20.2 *vs* 24.1 cases/1000 person years; hazard ratio 0.85; 95% confidence interval 0.74

to 0.97). The disparity between dementia and mild cognitive impairment was probably due to the low event rate because the main study was stopped earlier than originally planned, due to positive findings with regard to cardiovascular events [72••].

The MRI findings from SPRINT-MIND involved a subset of subjects given a brain MRI at baseline and the study conclusion [78•]. The findings of the primary analyses have been published in abstract form. It showed a significantly smaller increase in total brain white matter lesion volume favoring intensive treatment. Changes in total brain volume were larger in the intensive treatment group but this was not statistically significant. The reasons for this were unclear, and the findings indicated a significant gender difference in total brain volume change, but not in total white matter lesion volume change. Brain volume changes in women favored intensive treatment, the opposite of what was found in males. The underlying etiology for these changes in brain volume and gender differences is also unknown.

The findings from SPRINT-MIND are notable for several reasons. This is the first large study to show the value of vascular risk factor reduction in preventing cognitive decline (functionally defined as mild cognitive impairment). Mild cognitive impairment is the prodrome for both vascular cognitive impairment due to extensive white matter disease, as well as primary degenerative dementias such as AD. It can only be surmised that had the study continued, the differences in incidence of mild cognitive impairment would translate into lowered dementia risk with intensive BP control. The clinical findings also found a structural correlation in the volume of white matter lesions with smaller increases over several years in the intensive BP control group. As discussed below, the relationship of small vessel disease, the main underlying pathology of white matter disease to cognition, is complex, but all of the findings seem concordant with the popular mantra that "What is good for the Heart is also good for the brain" [79]. A pooled cohort results by Yaffe et al. confirmed that early adult and midlife hypertension is associated with greater risk of cognitive decline while very late life hypertension is associated with less cognitive decline [80].

Antihypertensive Use and Cognition

If lowering blood pressure can prevent cognitive impairment or improve cognition, another important question is if there are certain antihypertensives that provide better neuroprotection than others. Studies looking into this have shown mixed results. Two recent meta-analyses explored this association. Hughes et al. (2020) looked at 14 randomized clinical trials, 12 of which included the incidence of dementia or composite of dementia and cognitive impairment [81]. BP reduction with use of antihypertensive medications (AHMs) showed a reduction in incident dementia (OR 0.93 [95%CI 0.88–0.99] and cognitive decline (OR 0.93 [95%CI 0.88–0.99] over a 4.1-year follow-up period. Of note, lowering the BP did not show a significant association with reduction in cognitive test scores used in these studies. Ou et al. (2021) showed moderate evidence for AHMs and dementia risk reduction, with a 21% risk reduction compared to non-AHM users (RR: 0.79, [95%CI 0.70–0.89]) [8••]. The type of AHM did not seem to matter, as the risk reduction was seen in all the AHMs analyzed in this study, including thiazide diuretics, calcium-channel blockers, and ACE inhibitors. A duration of 5 years of AHM seemed to confer the greatest protective effect against dementia (RR: 0.56 [95% CI 0.37–0.86]) and AD (RR: 0.57 [95%CI 0.35–0.91]) [8••].

Two AHM classes in particular, calcium channel blockers (CCBs) and those that affect the renin-angiotensin aldosterone system (i.e. ACE inhibitors and ARBs), have shown promise in a few meta-analyses that indicate these medication classes might exhibit additional protection against dementia than can be accounted for in their BP-lowering mechanisms. Starting with CCBs, the evidence is mixed, with some studies by Feldman et al. showing reduction in dementia risk in subjects > / = 60 years of age with amlodipine [HR 0.61 [0.49–0.77]) [82]. Other longitudinal studies such as the Baltimore Longitudinal study of aging have shown no such neuroprotective effect of CCBs nor lowered risk of AD [83]. A 2014 meta-analysis found no such protective benefit as well [84]. A 2018 meta-analysis of 10 prospective studies did show positive results with CCBs and incident dementia, with a risk reduction of 30% compared to those not using CCBs [85]. While dihydropyridine CCBs showed a larger risk reduction of 44% [RR: 0.56, [95%CI 0.40–0.78]), compared to 19% with non-dihydropyridine CCBs (RR: 0.81 [95%CI 0.57–1.15]) although this class difference was not statistically significant. Postulated mechanisms for CCBs potential role in neuroprotection include blocking intracellular calcium entry and halting neuronal apoptosis [86]. Another potential mechanism, especially for the dihydropyridine CCBs, is modulation of amyloid precursor protein processing and the promotion of beta-amyloid clearance across the blood–brain barrier [87].

There is also growing evidence as to the importance of the renin-angiotensin system (RAS) in AD. A distinction between systemic and brain has been characterized, with angiotensinogen formed in the CNS in astrocytes, being cleaved by angiotensin converting enzyme into angiotensin, the effector molecule [88]. The brain RAS has been implicated in a variety of CNS activities, including stress, memory, anxiety, depression, and even neurodegeneration. Animal models exploring brain RAS

and neurodegeneration further: use of ACEIs has shown improved cognitive function, reduction in beta-amyloid peptide levels, prevention of cognitive decline, and promotion of hippocampal synaptic activity. Similar cognitive benefits have been seen with angiotensin receptor blockers (ARBs). At the receptor level, activation of angiotensin II receptors (ATII) has shown to enhance neuroinflammation, beta-amyloid accumulation, and inhibition of acetylcholine release. From a clinical standpoint, ACEIs and ARBs have been shown to slow cognitive decline when compared to non-RAS AHMs [88]. Li et al. showed a greater reduction in dementia risk for its cohort who received ARBs (0.76 [95%CI 0.69 to 0.84]) compared to lisinopril (0.81, [95%CI 0.73 to 0.90)] [89]. The combination of ARBs and lisinopril provided an additive effect that reduced the risk of incident dementia and nursing home admissions.

Barthold et al. showed that RAS associated AHMs (ARBs and ACEIs) provided greater protection against incident dementia in men only (OR: 0.931, [CI: 0.895–0.969]) [90]. ARBs were shown to be superior in dementia risk reduction compared to ACEIs, with statistically significant effects only seen in white men and white and black women. A meta-analysis conducted from Ye et al. (2015), looking at 12 studies with 896,410 participants, looked at the use of RAS-associated AHMs and showed a reduced rate of AD incidence of 19% (HR 0.81, [95%CI 0.72–0.92)] [91]. This study also showed a slowing in cognitive decline when both observational and randomized controlled trials were combined; however, this did not hold when isolating the randomized controlled trials.

A meta-analysis conducted by Scotti et al. included 15 studies (13 cohort studies, 2 case–control studies), comparing RAS-AHMs, beta-blockers, and CCBs [92•]. This study found that RAS-mediating AHMs reduced risk of any dementia by 22%, which included AD and vascular dementia; however, this risk reduction was statistically significant for ARBs, not ACEIs. The ARBs did not achieve statistical significance with vascular dementia when treated separately. While the current data on ARBs, ACEIs, and CCBs seem promising, more robust clinical data is needed before these agents can be recommended over others.

Future Considerations

While most clinical trials have focused on the use of antihypertensives in the prevention and mitigation of dementia, there is growing interest in exploring the microvascular milieu in greater detail in the hopes of developing novel therapies that potentially can reverse damage inflicted on the microvasculature modulated through disease and the aging process. Some of these therapeutics target mitochondrial function by removing reactive oxygen species as well as promote mitochondrial energy capacity [93, 94]. Another class of therapies used in animal models is "senolytics," which clear aged (i.e., senescent) cells to promote regeneration [95].

Conclusion

The relationship between blood pressure control and reducing the risk of cognitive decline is complex. Blood pressure control should be longitudinally studied in combination with other measures to control other modifiable vascular risk factors like high blood glucose level and high cholesterol. We need future studies with a higher number of participants to integrate different measures controlling vascular risk factors and encourage physical activity to develop a comprehensive approach which could serve as a preventive strategy against cognitive decline.

In conclusion, there are multiple strands of both empirical evidence of effects of HTN and its treatment on the neurobiological substrates and clinical development of cognitive impairment and dementia. Given the aging of the overall population in developed and developing countries, these relations need to be translated into clinical practice, where applicable, in order to lessen the expected increase in prevalence of cognitive impairment in older populations, especially those showing systemic morbidity traceable back to prolonged hypertension.

Compliance with Ethical Standards

Conflict of Interest Joseph E. Malone, Mohamed I. Elkasaby, and Alan J. Lerner declare that they have no conflict 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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- • Of importance
- •• Of major importance

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