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Review

Hypertension and cognitive dysfunction: a review of mechanisms, life-course observational studies and clinical trial results

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Hypertension is one of the most prevalent vascular risk factors and a leading cause of disability and mortality worldwide. The negative impact of hypertension on brain health is substantial. Already well-established as a risk factor for cerebrovascular disease, hypertension also has been shown to increase the risk for cognitive impairment and dementia. Mounting evidence from epidemiological studies suggests that hypertension, particularly in midlife, is associated with late-life cognitive impairment and the development of dementia. The link between late-life hypertension and cognitive function is, however, less clear. Experimental and neuroimaging studies have revealed complexities of mechanisms underlying the link between hypertension and cognitive function. Furthermore, the effect of blood pressure lowering on cognitive function, the optimal target and timing of the intervention, and the optimal antihypertensive agent in the context of cognitive function remain unclear. In this review, we discuss contemporary science on the link between hypertension and cognitive function by reviewing experimental, neuroimaging, and life-course observational studies. Furthermore, we provide a detailed review of randomized clinical trials addressing the effect of blood pressure lowering on cognitive function. Finally, unanswered questions, challenges, and other considerations for blood pressure lowering are highlighted.

Keywords

Hypertension; Blood pressure; Dementia; Cognition; Alzheimer's disease; Risk factors; Antihypertensive; Clinical trial

1. Introduction

Vascular risk factors and related disorders contribute to cognitive decline and Alzheimer's disease-related dementias [1, 2]. Chronic hypertension has emerged among vascular risk factors, as a major contributor to adverse cognitive outcomes [3]. Particularly, evidence from observational studies has established a strong link between hypertension during midlife and negative cognitive outcomes in later adulthood [4, 5]. Furthermore, recent life-course observational studies have shown a link between raised blood pressure as early as young adulthood and worse cognition in midlife [6, 7].

Given that hypertension is a modifiable vascular risk factor, it represents an important target for preventive and treatment interventions to mitigate dementia risk. A number of major clinical trials has shown that lowering blood pressure reduces morbidity and mortality associated with cardiovascular diseases and stroke [8]. However, similar beneficial effects on cognition and dementia risk have not been consistently reported [3, 9, 10]. In fact, the impact of lowering blood pressure on cognitive function in older age is less clear and remains a matter of debate. Furthermore, the precise blood pressure lowering target in different age categories remains controversial as some experts suggest less stringent blood pressure lowering in the elderly to preserve cerebral autoregulation [11]. Therefore, a deeper understanding of the complex relationship between hypertension and brain structure and function is essential and will help identify potentially effective therapeutic targets.

In this review we provide discussion of the following relevant topics that link hypertension to cognitive outcomes: (1) Pathophysiology underlying the association with a focus on hypertension-induced cerebrovascular alterations and role of the renin-angiotensin system (RAS) and neuroimaging markers; (2) Observational studies across the life course; (3) Study designs and results of blood pressure lowering in randomized controlled trials (RCTs); and (4) Guidance statements, blood pressure lowering targets, and unanswered questions and challenges going forward.

2. Pathophysiology underlying the link between hypertension and cognition

The mechanisms underlying the link between hypertension and cognitive impairment are complex and diverse. Current evidence suggests that the synergistic interaction between multiple pathologic factors is likely responsible for hypertension induced cognitive impairment. A detailed review of this topic has been previously provided by the 2016 American Heart Association statement and others [3, 9, 11, 12]. Below we provide a brief summary of key points, and summarize current evidence using neuroimaging markers to elucidate the link between hypertension and cognition (Fig. 1).

The large and small cerebral vessels are the prime targets of hypertension in the brain. Hypertension results in struc-

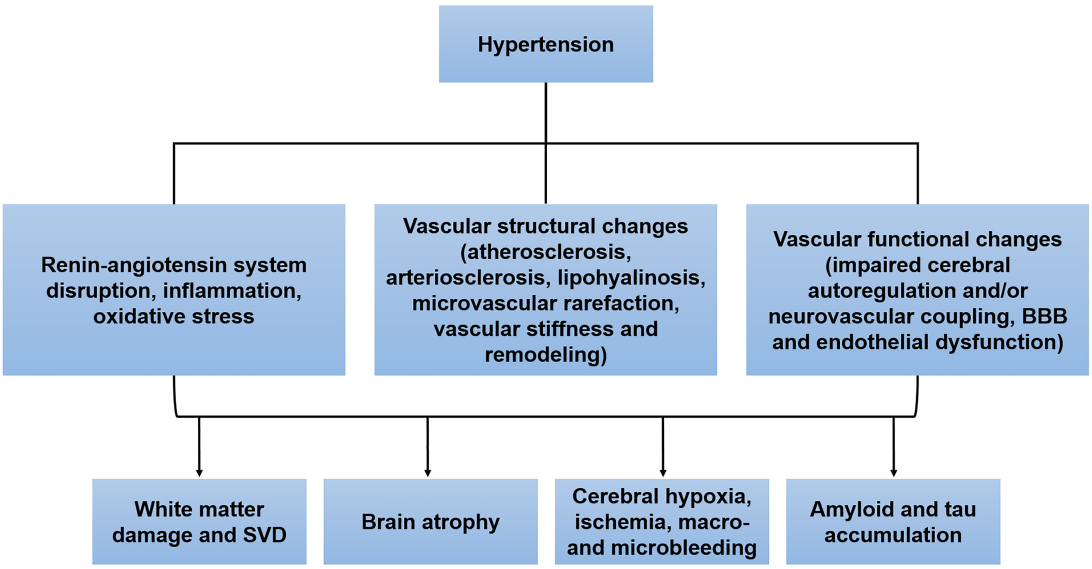

Fig. 1. Mechanisms linking hypertension with brain health. Hypertension results in cerebrovascular structural and functional alterations, disruption in the renin-angiotensin system's function, inflammation, and oxidative stress. Such hypertension-induced alterations may compromise brain health by predisposing brain to white matter damage and cerebral small vessel disease, brain atrophy, cerebral macro- and microbleeds, brain ischemia/hypoxia, and deposition of pathologic proteins in the brain. All of the aforementioned brain lesions have been shown to negatively affect cognitive function.

tural and functional alterations in cerebral vessels, which, in turn, predispose brain to white matter damage, brain atrophy, cerebral macro- and microbleeds, brain ischemia and deposition of pathologic proteins. All of the aforementioned brain lesions have been shown to negatively affect cognition and increase the risk for cognitive impairment [11] (Fig. 1).

2.1 Vascular structural changes

Blood flow to the brain is controlled by segmental vascular resistance in and around the brain [13]. Vessels primarily outside the brain including pial arterioles and large arteries, provide approximately 60% of the vascular resistance, and penetrating arterioles, capillaries and venules provide about 40% of the vascular resistance. When there is hypertension, cerebral vessels undergo adaptive structural changes in response to hypertension to protect downstream smaller vessels from the mechanical stress associated with increasing pressure. However, such adaptive structural changes may become maladaptive over time, resulting in various pathologies [12]. The interaction between several mechanical, humoral, and cellular factors—such as endothelial damage, inflammation, oxidative stress, and calcium deposition—are likely responsible for structural changes in cerebral vessels [14, 15]. Such structural changes in the setting of hypertension include atherosclerosis of larger cerebral arteries, arteriosclerosis, lipohyalinosis, microvascular rarefaction, hypertrophic and eutrophic vascular remodeling, and vascular stiffness [3, 11]. In particular, cerebral small arteries and arterioles are more vulnerable to the mechanical stress associated with hypertension [16, 17]. Alterations in these small vessels supplying the subcortical white matter may ultimately lead to cerebral small vessel disease (cSVD), which is a significant contributor to white matter damage, silent brain infarcts and clinically manifest lacunar strokes [3, 10, 11, 16, 17]. All these structural changes, in concert with alterations in cerebrovascular function, contribute to brain dysfunction and may ultimately lead to cognitive impairment.

2.2 Vascular functional changes

Hypertension may adversely impact cerebrovascular functioning by disruption in neurovascular coupling, cerebral autoregulation, and endothelium-dependent mechanisms. Neurovascular coupling is a normal physiologic response to neuronal activation that results in a localized increase in cerebral blood flow. This mechanism is regulated by endothelial cells, neurons, astrocytes, and vascular smooth muscle cells. Chronic hypertension has been shown to attenuate the increase in cerebral blood flow in response to neuronal activation, thus creating a mismatch between metabolic demand and blood flow delivery [16, 18]. Such perfusion mismatch is thought to contribute to cognitive impairment, although direct data examining the link between hypertension and loss of neurovascular coupling in humans is lacking. Cerebral autoregulation, another normal physiologic mechanism in the brain, is a regulatory mechanism that ensures relatively constant cerebral blood flow over a wide range of blood pressure fluctuations, which is likely mediated by neurogenic, myogenic and metabolic mechanisms [19]. In the setting of chronic hypertension, there is a rightward shift in the autoregulatory curve, which creates vulnerability to sudden changes in blood pressure resulting in ischemia and increased risk for brain hemorrhage [10, 11]. Direct data examining the link between hypertension and cerebral autoregulation in the context of cognitive impairment in humans are warranted.

A recent study in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort showed that exposure to a higher burden of vascular risk factors—including higher blood pressure levels—during young adulthood is linked with worse cerebral autoregulation during midlife as measured by transcranial Doppler ultrasound [20]. These results, albeit limited, support the notion that impaired cerebral autoregulation is a likely early mechanism underlying the link between higher blood pressure and negative cognitive outcomes. Finally, hypertension has been shown to disrupt the function of endothelial cells. Endothelial cells are critical in the regulation of microvascular blood flow, blood-brain barrier function, and protecting the vessels against thrombosis, atherogenesis, and accumulation of vascular amyloid β [3, 21]. Disruption in endothelial function in the setting of hypertension may contribute to reduced cerebral blood flow, atherosclerosis, and accumulation of harmful proteins in the brain, all of which may negatively impact cognitive function [3].

2.3 Renin-angiotensin system (RAS)

Emerging evidence supports the involvement of RAS in hypertension-induced brain injury and points toward the potential impact of drugs within this family to prevent dementia [10]. RAS is a complex system of interconnected hormones and receptors involved in the regulation of important physiologic functions such as water and electrolyte balance, hemodynamic hemostasis, and blood pressure. However, chronic activation of this system may lead to endothelial injury, oxidative stress, and inflammation, which in turn leads to various pathological conditions such as hypertension [22]. Although RAS was initially believed to be mainly localized to the systemic circulation, further research has revealed locally expressed RAS in a number of tissues including the brain [23]. In fact, all components of RAS are known to be locally produced in several brain regions and contribute to hypertension development and hypertension-induced brain injury [23–26]. It has been shown that angiotensin II (Ang-II) in the brain—the main vasoactive peptide of RAS—promotes a hypertensive state by altering sympathetic neural outflow, the release of hormones involved in homeostasis regulation and inflammatory processes [24]. Ang-II in the brain is known to function through binding to two major receptors: Ang-II type I receptor (AT1) and Ang-II type II receptor (AT2). It is generally believed that the AT1 receptor mediates most of the hypertensive effects of Ang-II, while the AT2 receptor possesses opposing effects by promoting vasodilation, antiproliferation, and increase in cerebral blood flow [23–25]. Activation of the Ang-II/AT1 axis has been shown to result in vascular remodeling, fibrosis, and vascular stiffness in the brain. In addition, Ang-II was shown to impair cerebrovascular function through its negative effects on cerebrovascular autoregulation, and inducing endothelial dysfunction and blood-brain-barrier breakdown [27, 28]. However, blockade of the AT1 receptor or angiotensin converting enzyme (ACE) was shown to reverse cerebrovascular dysfunction induced by hypertension [29] and improve endothelial cells' barrier function via activation of AT2 receptor signaling [30, 31]. Interestingly, the AT1 receptor and ACE signaling were also linked with exacerbation of cell death in brain regions involved in cognitive function through initiating a cascade of oxidative stress processes in animal models [25]. The AT2 receptor activation, however, was shown to facilitate cognition and cell survival and possess antioxidant and anti-inflammatory functions [25]. Furthermore, experimental data suggest that the RAS in the brain may regulate processes beyond BP control including learning and memory behaviors [25]. Taken together, emerging evidence support the possible role of centrally acting RAS in hypertension-induced cognitive impairment. However, the interaction between systemic and centrally acting RAS remains largely unknown.

Given the negative effects of RAS on cerebrovascular function and structure in the setting of hypertension, modulation of RAS has been a target to study in relation to its impact not only on blood pressure lowering, but also on cerebrovascular outcomes [32]. Modulation of RAS has been documented to have a protective effect on cognitive function in various experimental models of cognitive impairment such as Alzheimer's disease's (AD) models, hypertensive animals, and post-stroke cognitive impairment [26]. In humans, observational studies have provided evidence that RAS modulators are protective against incident stroke [32], cognitive function, and incident dementia [25, 26]. A meta-analysis on the impact of antihypertensive use on cognition that combined results from both observational and RCT studies showed that Ang-II receptor blockers (ARBs) had a greater beneficial effect on cognitive function than β-blockers, diuretics, and ACE inhibitors [33]. In the Alzheimer's Disease Neuroimaging Initiative (ADNI) study among 1629 individuals aged 55–99 years, blood pressure treatment with blood-brain-barrier crossing ARBs (telmisartan, candesartan, and valsartan) was associated with better cognitive function and less white matter hyperintensity (WMH) volume over 3 years of follow-up, compared to other antihypertensive drugs and RAS modulators that do not cross blood-brain-barrier [34]. Using observational data of 784 individuals with mild cognitive impairment (MCI), it was also shown that treatment with either ARBs or ACE inhibitors was associated with slower conversion to AD at 3 years follow-up, compared to other antihypertensives (33% vs 40%) [35]. Moreover, evidence from clinical trials suggest that RAS inhibitors reduce the risk for stroke even beyond the degree expected from the corresponding blood pressure reduction [32]. Given that current RCTs have not provided a clear benefit of RAS modulators on cognitive outcomes (see section 4.0 below for a review of RCT studies), more focused studies are warranted by targeting mechanisms by which RAS may influence cognition, such as oxidative stress and AT2 receptor stimulation [25].

2.4 Evidence from neuroimaging studies

Over the past few decades, neuroimaging studies have played a significant role in advancing our knowledge about

the mechanisms underlying the link between hypertension and negative cognitive outcomes. Various neuroimaging markers, including brain volume, radiographic markers of cSVD such as WMH, neuronal connectivity, and brain amyloid β accumulation, have been studied in the context of hypertension induced cognitive impairment. Higher blood pressure values have been consistently shown to be associated with lower total and regional brain volumes [36–39] and greater reduction of total brain volume over time using magnetic resonance imaging (MRI) [40]. An age-dependent association between blood pressure and brain volume also has been implicated by studies showing a reverse link between blood pressure and brain volume among older adults. For instance, Foster-Dingley *et al.* [41] showed that among older adults (mean age 81 $\pm$ 1 years old) on antihypertensive treatment with mild cognitive deficits (median Mini-Mental State Exam [MMSE] score = 26), lower systolic and diastolic blood pressure (SBP and DBP) were associated with lower volumes of thalamus and putamen compared to higher blood pressure levels. However, in the CARDIA study among young and middle-aged adults, worse cardiovascular health during early adulthood and hypertension in midlife were both associated with lower total brain volume, higher abnormal white matter volume and worse white matter integrity in midlife [38, 39]. More recently, morphometric changes of the brain have also been linked with higher cumulative exposure to blood pressure during early adulthood. It was shown that higher cumulative exposure to SBP during young adulthood is associated with inward deformity in the left lateral caudate head and lateral nucleus accumbens, the right lateral pallidum and thalamus, and the medial and lateral putamen during midlife [42]. Taken together, these findings support the notion that structural and morphometric changes of the brain, which are known to impact cognitive function, may be earlier signatures of future hypertensive induced cognitive impairment.

Neuroimaging markers of cSVD that manifest on MRI, such as WMH, lacunar infarcts, and cerebral micro-bleeds, have been all shown to have a strong relation with hypertension [9]. In particular, WMH on MRI has been established as a radiographic measure of hypertensive brain injury. Hypertension has been associated with higher WMH volume [43] and greater progression of WMH burden [44]. Moreover, WMH progression has also been associated with a greater decline in cognitive function [45]. Together, these findings suggest that white matter in the brain may be particularly vulnerable to the negative impact of hypertension. Moreover, accumulating evidence from newer imaging and analysis techniques, such as diffusion, kurtosis, free water, and myelin imaging, suggest that WMH represents the end of a continuous spectrum of white matter injury [46–50]. In fact, microstructural changes in normal appearing white matter may be measured long before they manifest as WMH on standard neuroimaging studies [51, 52]. Hypertension has been associated with worse white matter diffusion properties and microstructural integrity [53], and these associations appear to be largely independent of WMH volumes [54]. Similarly, accumulating evidence links cognition with white matter microstructural integrity as measured by diffusion imaging [55, 56]. In line with these, our recent results from the CARDIA cohort showed that higher exposure to SBP from young adulthood to midlife was associated with changes in diffusion properties of normal appearing white matter among middle aged adults without a significant burden of WMH [57]. Therefore, the health or integrity of the white matter, and even normal appearing white matter on MRI, may be a significant factor contributing to or leading to hypertension induced brain injury.

Finally, hypertension has been associated with AD specific markers on neuroimaging, such as cortical thickness on MRI and amyloid β deposition on Positron emission tomography (PET) imaging. Although some cross-sectional studies have reported a positive relationship between hypertension and greater amyloid β accumulation in the brain [58, 59], others have failed to show this relationship, particularly when blood pressure was assessed in midlife and early adulthood [60–62]. For example, recent cross-sectional analyses of cognitively normal and AD patients aged 55–90 years showed that among cognitively normal individuals, hypertension is associated with lower AD associated cortical thickness (including the middle temporal, entorhinal, inferior temporal, and fusiform gyrus on MRI) but not with brain amyloid β deposition on PET [63]. Among AD patients, however, hypertension was associated with lower brain amyloid β deposition but not with AD associated cortical thickness [63]. In another study, among 465 young to middle aged participants from mainland Britain, it was shown that higher blood pressure and greater increase in blood pressure during the 4th and 6th decade of life were associated with higher WMH and smaller brain volumes during the 6th and 7th decade of life (7% and 15% increase in WMH volume per 10 mm Hg increase in SBP and DBP, respectively). However, blood pressure during young to middle adulthood was not associated with brain amyloid β deposition in late adulthood [62]. In 322 cognitively normal participants (mean age = 52 years) in the Atherosclerosis Risk in Communities (ARIC) cohort, greater number of midlife vascular risk factors was associated with elevated brain amyloid β deposition more than 20 years later (odds ratio = 1.41 per additional increase in midlife vascular risk factors). However, blood pressure in midlife was not associated with brain amyloid β deposition in late-life [60]. Similarly, in 942 individuals from the Mayo Clinic Study of Aging, midlife hypertension was not associated with late-life brain amyloid β deposition. However, midlife hypertension was associated with late-life AD-pattern neurodegeneration, defined as cortical thickness in the middle temporal, entorhinal, inferior temporal, and fusiform gyri [61]. Therefore, it can be concluded that hypertension may contribute to AD primarily through a reduction in brain reserve but not through amyloidogenesis pathways. Interestingly, in a recent cross-sectional analysis of 1546 non-demented in-

dividuals with a mean age of 62 (40% female), it was shown that hypertension in midlife individuals (<65 years of age) was associated with higher cerebrospinal fluid levels of tau-related biomarkers. However, no correlation between blood pressure and cerebrospinal fluid levels of amyloid β protein was detected. Moreover, cerebrospinal fluid levels of tau protein were shown to mediate the link between hypertension and cognition in midlife, but not in late-life (11% to 17% mediating effect) [64]. These findings further support the notion that hypertension may contribute to AD development through amyloid β-independent pathways and highlight the need for future studies to better understand the mechanism underlying the relation between hypertension and AD development. That is, does hypertension directly lead to AD and neurodegeneration, or are there indirect pathways conferring additive risk to ongoing neurodegeneration?

3. Epidemiological evidence on the link between hypertension and cognition

Epidemiological evidence linking hypertension and its components—SBP and DBP—with adverse cognitive outcomes is plentiful. A large number of observational studies have established a strong link between hypertension and a range of adverse cognitive outcomes [65]. Cognitive outcomes studied in relation to hypertension include cognitive function/decline, MCI, and dementia and its subtypes. While cognitive function assessed by neuropsychological tests allows capturing more subtle changes in cognitive function, MCI or dementia are clinically relevant outcomes that have stronger public health implications [10]. Hypertension has been associated with all of these cognitive outcomes [4, 5, 66–68]. In addition, a role for incident hypertension, prevalent hypertension, and prehypertension in relation to cognitive deficits has been implicated. For example, in ~3000 middle-aged participants from the Vieillissement Sante' Travail (VISAT) study, Rouch *et al.* [69] showed that both prevalent and incident hypertension were linked with a steeper decline in global cognition. In the ARIC cohort, both hypertension and prehypertension were shown to increase the risk of incident dementia [70]. Similarly, ELSA-Brasil cohort results showed that hypertension and prehypertension were both associated with steeper decline in cognitive function (memory and verbal fluency) [71].

While epidemiological evidence clearly points toward a strong link between hypertension and worse cognitive outcomes, attention has been paid to the age-dependent impact of hypertension on cognition. Recently, results from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study showed that age modifies the relationship between blood pressure and cognitive change over a period spanning 8 years in older adults. It was shown that with increasing age, higher blood pressure values were associated with steeper global cognitive decline [72]. Furthermore, emerging evidence suggest that the negative impact of hypertension on cognitive outcomes may start as early as young adulthood, underscoring the need for primordial prevention of hypertension [73]. In line with this, the recent Lancet Commission statement indicates that hypertension in midlife, but not in late-life, is among the 12 potentially modifiable risk factors for dementia with a population attributable risk of 2% [74]. Given the importance of age at hypertension onset and its duration in relation to cognitive outcomes, below we summarize evidence from observational studies that focused on the relationship between hypertension—and its components—with cognitive outcomes according to different stages of life (Table 1).

3.1 Hypertension and cognition in early and middle adulthood

Substantial evidence from observational studies supports that high blood pressure in middle aged individuals <65 years of age, especially if left untreated, is associated with a higher risk of cognitive impairment 20–30 years later. The Honolulu-Asian Study (HAAS) provided early evidence that increasing SBP in midlife (53 $\pm$ 5 years old) is associated with an elevated risk of cognitive impairment approximately 25 years later [4]. In the HAAS study, for every 10 mm Hg increase in midlife SBP, there was a 9% (95% confidence interval [CI], 3% to 16%) increased risk of poor cognitive function, especially in those who were never treated with antihypertensives [4]. One of the largest studies (>10,000 participants) showing a link between midlife hypertension and late-life cognitive decline was the ARIC study [5, 75, 76]. In the ARIC cohort, hypertension and high SBP in midlife (45–64 years of age) were associated with a 20-year decline in processing speed, verbal fluency, and global cognitive function [5]. Moreover, the ARIC study results suggest that untreated hypertensives had a steeper decline in cognition compared to hypertensives on antihypertensive medication (effect estimates of –0.079 compared to –0.050) [5]. Results from the National Heart, Lung, and Blood Institute Twin Study [43], and the Male Cohort in Upsala study [77, 78] reported similar findings: higher blood pressure in middle aged men is related to steeper cognitive decline over a period spanning ten years [43] and poorer cognitive function 20 years later [77, 78]. Few studies reported a null association between midlife hypertension and cognitive function [79, 80]. However, these studies are limited by cross-sectional designs or a short duration of follow-up. For example, the REGARDS study did not find an association between hypertension assessed at 64 $\pm$ 9 years of age and cognitive function assessed only 40 months later [80].

Hypertension and higher blood pressure values (particularly SBP $\geq$140 mm Hg) in midlife have been also linked with a higher risk of late-life dementia. In the HAAS study, midlife SBP $\geq$140 mm Hg compared to SBP <120 mm Hg was associated with a higher risk of dementia over a 5-year follow-up time [66]. In the ARIC cohort, midlife prehypertension and hypertension were both associated with ~1.3-fold higher risk of dementia over a median follow-up of 23 years [70]. In the Framingham Offspring cohort, midlife (mean age 55 years) SBP $\geq$140 mm Hg was associated with a 1.6-fold higher risk

Table 1. Summary of key points from observational studies assessing the link between hypertension and cognitive impairment.

Hypertension is linked with negative cognitive outcomes according to duration of hypertension and life-course time period:
Midlife hypertension is strongly associated with late-life cognitive impairment/dementia.
Young-to-midlife higher blood pressure exposure is associated with midlife cognitive impairment.
The association between hypertension and cognitive outcomes in late-life is complex and less consistent.
Distinct patterns of blood pressure changes over the life-course may be important predictors of late-life cognitive impairment.

of dementia over 18 years of follow-up [81]. Moreover, high blood pressure in midlife has been consistently linked with an increased risk for incident AD and vascular dementia [82–84].

Taken together, growing evidence from epidemiological studies suggests a strong link between midlife hypertension and late-life cognitive deficits. These findings support the notion that the duration of hypertension during midlife may represent an important determinant of late-life cognitive deficits [9]. In line with this, longitudinal studies have shown that a greater duration of time since hypertension onset is associated with worse cognitive outcomes in late-life [85–87]. Moreover, blood pressure patterns during the life-course may play an essential role in cognitive functioning, as is discussed in section 3.3 below. However, there remains several unanswered questions that need to be addressed in future studies, such as (a) the optimal blood pressure level that is most protective of cognition in late-life, (b) the precise period during which blood pressure may be most deleterious for cognitive outcomes, and (c) the age-dependent effect across the life course of antihypertensive treatment on cognitive outcomes. Finally, to summarize the results of observational prospective studies on the link between hypertension and cognitive outcomes in midlife, it is worth noting the results of a recent systematic review and meta-analyses [65]. In this study, 209 prospective studies published until August 2019 were identified that reported the impact of blood pressure exposure on the risk of cognitive disorders in various stages of life, from midlife to late-life. This meta-analysis included prospective studies of participants with normal cognition or no MCI at baseline, resulting in ~2 million individuals included in the meta-analyses. The mean age of participants ranged from 35 to 93 years, and the mean duration of follow-up ranged from 1.5 to 43 years. Overall, this meta-analysis suggests that midlife blood pressure (defined at $<$65 years old) has a stronger impact on cognitive outcomes than late-life blood pressure. Specifically, this study suggests that according to longitudinal data: (1) midlife hypertension is associated with increased risk of impairment in global cognitive function and executive function, but not with memory; (2) midlife hypertension, SBP $\geq$140 mm Hg, DBP $\geq$80 mm Hg and DBP change of $\geq$5 mm Hg are associated with 37% to 52% increased risk of dementia, and (3) midlife hypertension and high DBP are associated with a higher risk of incident AD [65], where DBP $\geq$90 mm Hg is associated with a 1.51-fold increase in the risk of AD.

While most studies have focused on the link between midlife hypertension and late-life cognition, emerging evidence suggest that high blood pressure as early as childhood may negatively impact cognitive function. In the CARDIA study of young to middle-aged participants from their 20s to 60s years of age, it has been shown that cumulative years of elevated blood pressure beginning in young adulthood have a stronger impact on cognitive function [6, 7], as compared to a single blood pressure measurement in midlife [6]. In the same cohort, early-onset hypertension (at $<$35 years old), but not late-onset hypertension (onset at $\geq$35 years old), was shown to be associated with lower global cognitive function, executive function, and processing speed during midlife [87]. More recently, the Cardiovascular Risk in Young Finns Study results showed that consistently high SBP values from 9 to 49 years of age are associated with worse episodic memory and associative learning at 34–49 years of age [88]. Similarly, Yaffe *et al.* [89] showed that consistently elevated SBP values, especially in early adulthood, were associated with a greater decline in late-life global cognitive function and processing speed. Interestingly, in this study the link between high blood pressure in midlife and cognitive function in late-life was attenuated after controlling for early and late-life blood pressure values [89]. Together, these results suggest that the detrimental impact of hypertension on cognitive function may start even earlier than midlife and underscores the potential role for primordial prevention of hypertension in the quest to help maintain cognitive function as one age.

3.2 Hypertension and cognition in late-life

Studies on the relation between hypertension and cognitive outcomes in older adults have reported conflicting results. While some studies have reported a deleterious impact of hypertension on cognition, many others have failed to find such a relation. For example, results from the Cardiovascular Health Study [90], Framingham Heart Study [91], and Northern Manhattan study [92, 93] in older adults 65–75 years of age suggest that hypertension is associated with a decline in global cognition, executive function, processing speed, and memory. However, in individuals with a mean age of 74 $\pm$ 6 years from the Chicago Health and Aging study, blood pressure was not associated with a change in cognitive function over 6 years [94]. Similarly, cross-sectional results from the Italian Longitudinal Study on Aging [95] and East Boston study [96] of older adults $\geq$65 years of age did not show a relationship between blood pressure and cognitive function.

On the other hand, other evidence suggests a curvilinear U-shaped or J-shaped association between blood pressure and cognition in late-life [67, 97–101]. Recent results from the 'Septuagenarians, Octogenarians, Nonagenarians Investigation with Centenarians' (SONIC) study among community-dwelling older Japanese showed that higher SBP is associated with lower cognition only among 70-year-olds, while among 90-year-olds, the opposite was found [102]. Glyn *et al.* [67] showed that in those aged 65 to 102 years, both SBP <130 mm Hg or ≥160 mm Hg was associated with worse cognitive function as measured using a mental status questionnaire. Similarly, a curvilinear association between blood pressure and cognitive function was reported in a cross-sectional study of ~5800 participants aged 65–104 years of age, where both SBP <100 mm Hg and >140 mm Hg were associated with lower MMSE scores [97].

Hypertension in the 7th decade of life has been shown to increase the risk of MCI [93], while no strong link between hypertension and risk of dementia has been reported. By contrast, most studies support an association between low blood pressure and increased risk of dementia in late-life. For example, in a pooled analysis of adults aged 55–85 years from the Rotterdam study and the Göteborg H-70 study, higher blood pressure was associated with reduced risk of dementia in antihypertensive medication users [103]. The Kungsholmen project showed similar results. Lower DBP increased the risk of dementia and AD, especially in those taking antihypertensives or carriers of the Apolipoprotein E (APOE) e4 allele [104]. In the Bronx Aging Study, low DBP was associated with a 2-fold higher risk of dementia and AD among adults >75 years of age [105].

Only a few studies have assessed the link between hypertension and dementia subtypes, including vascular dementia among older adults [83, 103, 106, 107]. However, results are conflicting, showing both a positive relationship between hypertension and future development of vascular dementia [83, 106] or no relationship [103, 105, 107, 108]. It has been suggested that the relation between blood pressure and vascular dementia is age-dependent, such that high SBP is associated with increased risk of vascular dementia only between ages of 30 to 70, but not after 70 years of age [109]. It may be challenging to elucidate the relationship between hypertension and dementia subtypes as there is a high prevalence of mixed neuropathologies among cases of dementia [110], making such distinction between dementia subtypes difficult.

Taken together, observational evidence on the relation between blood pressure and cognitive outcomes in late-life does not show a consistent pattern. In fact, it appears that the link between blood pressure and cognition is largely dependent on the age at which blood pressure is assessed and the interval between blood pressure and outcome assessment. Furthermore, a non-linear curve may better explain the link between blood pressure and cognition in late-life. Such diverse findings in studies of older adults could be attributed to heterogeneous study populations, varied length of follow-up time, effects of specific classes of antihypertensive medications, or the confounding effect of other co-existing vascular risk factors in older adults. Finally, it should also be noted that other blood pressure components such as blood pressure variability and orthostatic hypotension may play a significant role in relation to cognitive deficits in late-life. Both blood pressure variability and orthostatic hypotension are more prevalent with increasing age and have been linked to cognitive deficits [111, 112].

In summary, taking into account the results from observational studies on hypertension and cognitive outcomes in old age and results from a recent meta-analysis [65] of prospective cohort studies up to August 2019, the totality of data suggest that in late-life (defined as those >65 years old): (1) hypertension may not be related to the risk of dementia and AD, but is associated with progression from MCI to all-cause dementia and worse episodic memory, (2) high SBP is not associated with risk of dementia, whereas excessively high SBP ≥180 mm Hg increases the risk of dementia by 1.45-fold (95% CI of 1.03–2.06), (3) high DBP ≥90 mm Hg is associated with a 23% reduced risk of dementia, (4) there is a U-shaped relation between DBP and AD where optimal DBP levels are ~90 to 100 mm Hg for lower AD risk, and (5) excessive blood pressure variability and orthostatic hypotension are associated with increased risk of dementia, while pulse pressure does not seem to play a role.

3.3 Patterns of blood pressure over the life-course and cognitive outcomes

Several studies have identified the pattern of blood pressure changes over the life-course as an important determinant of cognitive outcomes. The Adult Changes in Thought study showed that in those aged 65–74 years who later develop dementia, SBP is consistently high but also has a steeper decline two years prior to dementia diagnosis [113]. However, among those aged >75 years who later developed dementia, SBP consistently fell without any particular patterns [113]. Similarly, the Kungsholmen project among dementia-free individuals aged ≥75 years showed that both SBP and DBP start to decline two–three years prior to a diagnosis of dementia and continue to decline thereafter [114, 115]. The HAAS and Prospective Population Study of Women in Gothenburg (PSW) cohorts showed similar patterns: a pattern of steeper rise in blood pressure in midlife followed by steeper decline after around 78 years of age in those who developed dementia [116, 117]. The PPSW study also showed that those who were on antihypertensive medications had a steeper rise in blood pressure in midlife, but also an earlier and steeper decline in blood pressure compared to those not on antihypertensive treatment [117]. These results were recently confirmed in the ARIC cohort [118]. The ARIC cohort included 4761 individuals aged 44–66 years at baseline (59% women, 21% Blacks) and 66–90 years of age at follow-up. This study showed that those with hypertension from midlife to late-life, and those with a 'midlife hypertension—late-life hypotension' pattern have 1.49- and

1.62-fold increased risk of subsequent dementia diagnosis, respectively [118]. Similar results were reported in the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, where a pattern of midlife hypertension and late-life lower DBP were associated with worse memory function in late-life [119]. More recently, Cheng *et al.* [120] assessed the link between BP trajectory changes 3 years before the diagnosis of dementia in the Chinese Longitudinal Healthy Longevity Survey study. Among >10,000 individuals aged ≥60 years, stabilized SBP group (defined as SBP declining from 175 to 135 mm Hg, 6% of the population) was associated with a higher risk of dementia compared with normal and elevated SBP groups (the normal group was defined as SBP at 135 mm Hg, and the elevated group was defined as SBP rising from 135 to 175 mm Hg) [120]. Overall, current evidence suggests that hypertension in midlife, and a pattern of high blood pressure in midlife and low blood pressure in late-life are associated with impairment of cognitive outcomes [121]. There is limited evidence linking blood pressure trajectory changes and dementia subtypes, including vascular dementia and AD. Few studies that addressed this question include the HAAS and PSW studies. In the HAAS study, the trajectories of SBP changes were greater in those who developed vascular dementia than those who developed AD [116]. The PSW study showed a similar pattern of rising in SBP followed by a sharper fall in SBP in those with all-cause dementia, AD, and pure AD [117].

Few studies have focused on patterns of blood pressure starting from early adulthood (e.g., <40 years of age). Recently, Hakala *et al.* [88] have identified the patterns of blood pressure exposure from 9 to 50 years of age among 3596 individuals. In this study, 5 SBP patterns were identified: (1) low-stable with consistently low SBP (18% of individuals), (2) normal-stable with consistently <120 mm Hg (40% of individuals), (3) moderate-stable with SBP level consistently ~120 mm Hg (17% of individuals), (4) moderate-increasing with normal SBP in childhood but continuously increasing from youth to midlife (20% of individuals), and (5) elevated-increasing with elevated SBP in childhood and continuously increasing blood pressure throughout adulthood (6% of individuals). Results suggest that the elevated-increasing SBP group had worse cognitive performance in midlife (β = –0.262 [–0.52, –0.005]) [88]. In another recent study, Yaffe *et al.* [89] reported the trajectories of SBP from early adulthood to late-life, and its association with late-life cognitive function using pooled analyses of four large prospective cohort studies. In this study of ~15,000 individuals aged 20 to 90 years old, SBP values were low in early adulthood, increased during mid to late-life, and continued to increase steadily into late life. Elevated SBP values, especially in early adulthood, were associated with a greater decline in late-life global cognitive function and processing speed [89]. Midlife high blood pressure was also associated with late-life cognitive decline, but this association was attenuated after controlling for early and late-life blood pressure values [89].

In summary, current evidence suggests that there may be different patterns of blood pressure exposure from childhood to late-life in relation to cognitive outcomes. While during mid to late-life a pattern of high followed by low blood pressure appears to negatively impact cognition [121], in earlier adulthood, a pattern of consistently elevated blood pressure seems to be a dominant pattern for negative cognitive outcomes. Given that the early and middle adulthood periods are less likely to be confounded by the effect of medication use and other co-existing vascular risk factors, patterns identified in these stages of life may be prone to less observational study bias. Finally, the characterization of risk for cognitive deficits according to blood pressure patterns may need to be integrated into future risk assessment studies for better identification of those at higher risk of dementia.

4. Clinical trials: blood pressure lowering, antihypertensive medications, and preservation of cognitive function

As the most important contributor to the global burden of disease, one of the most important modifiable risk factors for cardiovascular disease, and one of the largest contributors to morbidity and mortality worldwide, hypertension is an ideal target for the study of preservation of cognitive function [122, 123]. In this section, we review RCT designs and results of blood pressure lowering studies to prevent cognitive impairment or decline. In addition, we discuss key systematic analyses and meta-analyses of blood pressure lowering and cognition. We first discuss two recent high impact studies that may be considered companion trials, Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT MIND) and Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes (ACCORD MIND).

4.1 SPRINT MIND

4.1.1 Design

SPRINT MIND is arguably the most influential of the blood pressure lowering studies designed to preserve cognition. SPRINT MIND is a sub-study of a parent study, the RCT SPRINT, and assessed the effect of intensive SBP lowering (goal: <120 mm Hg) versus standard treatment (goal: <140 mm Hg) on prevention of MCI and dementia among 9361 participants [124]. The parent study was stopped early based on benefit of the intensive blood pressure lowering strategy on the primary composite of cardiovascular outcomes and all-cause mortality. The primary outcome of SPRINT MIND was the occurrence of probable dementia, and the secondary outcome included MCI and a composite of MCI or probable dementia. An expert panel adjudicated cognitive outcomes. Participants were 50 years of age or older, had a SBP between 130 and 180 mm Hg, and had increased cardiovascular risk, but were excluded from the study if they lived in a nursing home, had a diagnosis of dementia or were treated with medications for dementia, or had diabetes mellitus or a history of stroke [124]. Antihypertensive agents

were provided free of charge, all major classes of blood pressure lowering agents were included, and it was encouraged but not mandated to administer thiazide-type diuretics as a first-line agent, loop diuretics in those with chronic kidney disease, and beta-adrenergic blockers if there was coronary artery disease. Enrollment was between November 2010 and March 2013. The intervention period had a median of duration of 3.34 years, and the total follow-up time had a median duration of 5.11 years.

4.1.2 Main results

Of the 9361 participants who had a median age of 67.9 years, of which 3332 (35.6%) were women, adjudicated dementia occurred in 149 persons in the intensive treatment group and 176 in the standard treatment group representing 7.2 versus 8.6 cases per 1000 person-years, respectively, and a hazard ratio (HR) of 0.83 (95% CI of 0.67, 1.04) [124]. The risk of MCI, however, was significantly reduced by intensive SBP lowering as there were 14.6 versus 18.3 cases per 1000 person-years, respectively, and a HR of 0.81 (95% CI of 0.69, 0.95). Similarly, the combined outcome of MCI and probable dementia were statistically significantly reduced in favor of intensive SBP lowering treatment (20.2 versus 24.1 cases per 1000 person-years and a HR of 0.85, 95% CI of 0.74, 0.97) [124]. SPRINT MIND study follow-up continued for about 3 years after the main phase study was terminated, and the SBP differences between the treatment groups favoring intensive therapy went from 13 to 6 mm Hg.

The results have been met with enthusiasm in favor of intensive SBP lowering to maintain cognitive function. Due to the early study termination of the parent study, SPRINT MIND may have been underpowered for the primary endpoint probable dementia [124]. SPRINT MIND is undergoing an extension study which may help to clarify the results in relation to an underpowered primary outcome [123]. In a prior critique of SPRINT MIND, we recommended healthy skepticism about blood pressure lowering to prevent cognitive impairment or decline based on difficulty showing a beneficial effect in many other blood pressure lowering trials (described below in other sections) [123].

4.1.3 Substudy results

In a MRI sub-study of cerebral white matter lesions and total brain volume, intensive SBP lowering was associated with a smaller increase in cerebral white matter lesion volume but a greater decrease in total brain volume, although the absolute differences were minor [125]. In a domain-specific cognition sub-study of SPRINT and a median follow-up time of 4.1 years, there was no statistically significant difference in composite scores for memory; however, there was a steeper decline of processing speed in the intensive treatment group. The differences were slight, and possibly not clinically relevant [126]. Finally, in a sub-study of AD imaging biomarkers (hippocampal volume, regional atrophy, posterior cingulate cerebral blood flow, and mean fractional anisotropy of the cingulum bundle), there was a small but statistically significant reduction in hippocampal volume that was higher in the intensive SBP treatment group, consistent with the findings for total brain volume [127].

4.2 ACCORD MIND

4.2.1 Design

SPRINT MIND was patterned after ACCORD MIND with the main difference being the inclusion of patients with type 2 diabetes mellitus in the latter study [128]. ACCORD originally included an intensive glycemic arm (goal: hemoglobin A1c [HbA1c] $<6\%$) and a standard treatment arm (goal: HbA1c 7.0% to 7.9%); a lipid lowering arm in 53.8% of the total sample (placebo versus fenofibrate in participants with low-density lipoprotein cholesterol [LDL-c] levels <100 mg/dL); and a blood pressure lowering arm in 46.2% of the total sample of intensive (goal: SBP <120 mm Hg) versus standard (goal: SBP <140 mm Hg) treatment [128]. The intensive glycemic intervention was terminated as there was increased mortality in that group, and all patients were transitioned to standard glycemic treatment. The primary cognitive outcome was the Digit Symbol Substitution Test (DSST). The secondary cognitive outcomes were verbal memory and executive function. Cognition was assessed at baseline, and at 20 and 40 months, respectively, in 2977 participants, and brain MRI was evaluated at baseline and at 40 months in 503 participants.

4.2.2 Main results

The mean age of participants was 62 years, mean duration of type 2 diabetes mellitus of 10 years, and mean HbA1c level of 8.3%, and there were no differences in cognition at 40 months in either the intensive SBP lowering group or fibrate treatment group [128]. However, there was a statistically significant greater decline in total brain volume (by -4.4 cm^3; $p = 0.01$) at 40 months with intensive compared to standard SBP treatment. Parenthetically, stroke was statistically significantly reduced with intensive SBP lowering therapy in ACCORD [129] though this was not the case in SPRINT, whereby the latter study was underpowered for stroke outcomes, but numerically there were fewer strokes in the SPRINT intensive SBP lowering group [123]. In a separate analysis of a randomized open-label sub-study of ACCORD, intensive glucose lowering was associated with greater mean total brain volume at 40 months [130], however, by 80 months, there were no beneficial or adverse effects on cognition or brain MRI based on the ACCORD interventions. Notably, there was a loss of separation in therapeutic targets between the treatment groups [131]. By comparison, in ACCORD at 1 year mean SBP was 119.3 mm Hg and 133.5 mm Hg in the intensive and standard treatment groups, respectively.

4.3 Two studies that support lowering blood pressure to preserve cognition

We now discuss Systolic Hypertension in Europe (Syst-Eur) trial [132, 133] and Perindopril Protection Against Re-

current Stroke Study (PROGRESS) [134] as less recent RCTs that provide support for lowering blood pressure in the maintenance of cognition.

4.3.1 Syst-Eur

4.3.1.1 Design. Syst-Eur had a vascular dementia project which investigated whether lowering blood pressure could reduce the incidence of dementia [132]. Participants included in the study had no dementia at baseline, were 60 years of age or older, and had a blood pressure of 160–219 mm Hg/<95 mm Hg. Active treatment was nitrendipine with the possible addition of enalapril or hydrochlorothiazide or both drugs to achieve a SBP reduction of at least 20 mm Hg and below 150 mm Hg. Active treatment was compared to placebo. Cognition was assessed by the MMSE, and dementia was diagnosed if the MMSE score was 23 or less, and DSM-III-R (the Diagnostic and Statistical Manual of Mental Disorders, third edition) criteria were met. Dementia subtype was determined according to the modified ischemic score and consideration of brain imaging or by the Hachinski score.

4.3.1.2 Main results. Among 2418 randomized participants with a median follow-up of 2.0 years, the incidence of dementia was reduced by approximately 50% in favor of the active treatment group (7.7 versus 3.8 cases per 1000-patient years; 21 versus 11 patients; $p = 0.05$) [132]. The median MMSE score at baseline was 29 in both groups, and during the course of treatment the blood pressure was lower in the active treatment group (8.3 mm Hg/3.8 mm Hg). On average, MMSE scores did not change substantially in either treatment group, however, in control participants the MMSE score declined with declining DBP, but in the active treatment group, the MMSE scores had a marginal improvement with greater decline in DBP [132]. The investigators estimated that 19 cases of dementia might be prevented if 1000 hypertensive patients were treated for 5 years.

In an extended follow-up study to 3.9 years, active treatment reduced the risk of dementia by 55% (43 versus 21 cases; $p < 0.001$) [133]. Both AD and mixed or vascular dementia were reduced by active treatment. The authors concluded that the long-acting dihydropyridine calcium channel blocker protected older persons with systolic hypertension from dementia.

4.3.2 PROGRESS

4.3.2.1 Design. PROGRESS included 6105 participants (mean age of 64 years) with prior stroke or transient ischemic attack (TIA) [134]. The active intervention was perindopril with or without indapamide, a thiazide-like diuretic, and the comparator was placebo. The primary cognitive outcomes were dementia according to DSM-IV (the Diagnostic and Statistical Manual of Mental Disorders, fourth edition) criteria and cognitive decline defined by a drop of 3 points or more on the MMSE.

4.3.2.2 Main results. During a mean follow-up time of 3.9 years, dementia was diagnosed in 6.3% of the participants in the active treatment group and 7.1% of those in the placebo group (relative risk reduction 12%, 95% CI of –8%, 28%; $p = 0.2$) [134]. Cognitive decline was diagnosed in 9.1% of those in the active treatment group versus 11.0% of the placebo treatment group (risk reduction 19%, 95% CI of 4%, 32%; $p = 0.01$). In the active treatment group, there was a statistically significant reduction in the composite outcomes of recurrent stroke with dementia (34%, 95% CI of 3%, 55%; $p = 0.03$) and cognitive decline (45%, 95% CI of 21%, 61%; $p < 0.001$), but there was no clear effect amongst those who did not have recurrent stroke [134]. The combination of perindopril plus indapamide therapies resulted in blood pressure lowering of approximately 12/5 mm Hg, whereas perindopril therapy alone resulted in a blood pressure lowering of about 5/3 mm Hg [134]. Combination therapy had a greater effect on dementia than single therapy, however, the differences were not definitive in relation to dementia or cognitive decline. The authors concluded that blood pressure lowering with perindopril and indapamide should be considered for all patients with cerebrovascular disease.

4.4 Neutral studies of the relationship between blood pressure lowering or treatment and preservation of cognition

We summarize key elements of a number of RCTs that show neutral results in relation to blood pressure lowering and preservation of cognition in Table 2 (Ref. [135–143]).

4.5 Systematic reviews and meta-analyses of blood pressure lowering and cognition

We now briefly discuss recent systematic reviews and meta-analyses of blood pressure lowering or treatment and incident dementia or cognitive impairment. We have limited our review to publications in the past several years as these studies represent the most up-to-date sources and databases.

In 2019 on the occasion of the publication of SPRINT MIND, Peters and colleagues carried out a meta-regression analysis in light of the 8 completed RCTs that have included different approaches to blood pressure lowering and dementia endpoints [144]. Whereas none of the RCTs showed a clear beneficial effect, earlier studies that had higher baseline blood pressure and those with the greatest reduction of blood pressure from baseline might be expected to yield positive results. In fact, the difference in SBP levels ranged from 2 to 17 mm Hg. In meta-regression analysis (>40,000 participants from 8 studies), Peters *et al.* [144] showed that larger SBP lowering (≥10 mm Hg) was associated with a more substantial point estimate across the trials. SPRINT MIND was certainly congruent with the findings, and the meta-regression results provided moderately strong supportive evidence and no major harms in relation to blood pressure lowering. In a subsequent meta-analysis report, Peters and colleagues provided no clear and consistent evidence of any blood pressure lowering drug class being optimal for reducing the risk of incident dementia or cognitive decline (over 50,000 individuals

Table 2. Key elements of randomized controlled trials with neutral results in relation to blood pressure treatment or lowering and cognitive outcomes.

Study name (publication date)	Participant characteristic	Intervention	Cognitive outcomes	Main results	Key conclusions
SHEP* (1994) [135]	• N = 4736 • Mean age = 72 years (range 60 to 90 years) • 57% women, 14% Black • Blood pressure at baseline = mean 170.3/76.6 mm Hg • Follow-up time = mean 5 years	Active treatment with chlorthalidone (step 1), atenolol (step 2) or reserpine if atenolol contraindicated versus placebo.	Short-CARE administered at baseline and 6-month intervals for screening purposes, and once a cut-point is reached, the participant is referred for formal diagnostic evaluation. In addition, 2034 participants received a Part II evaluation of more specific cognitive tests.	• There were no differences between active treatment and placebo groups in cognitive impairment symptoms or mean changes between cognitive function tests. • The active treatment group had an 11–14 mm Hg lower SBP level throughout the trial.	Medical treatment did not cause deterioration in cognitive function in elderly persons with isolated systolic hypertension.
SCOPE** (2004) [136]	• N = 2098 (who did not receive additional antihypertensive therapy after randomization) • Mean age = 76 ± 5 • 66% women • Mean blood pressure at baseline = 1645 ± 9/75 ± 9 mm Hg • Follow-up time = mean 3.5 or 3.7 years. • Preserved cognitive function at baseline	Candesartan versus placebo.	Cognitive function and dementia were secondary outcomes (change in MMSE score, significant cognitive decline defined as ≥4 point reduction on MMSE score documented at 2 consecutive visits).	• The mean adjusted blood pressure reductions were 21.8/11.0 mm Hg in the candesartan group and 17.2/8.4 mm Hg in the placebo group resulting in an overall treatment difference of 4.7/2.6 mm Hg in favor of candesartan treatment. At the last visit, blood pressures were 144.1/80.0 mm Hg (candesartan group) and 147.6/81.9 mm Hg (placebo group). • There was no significant difference between the candesartan and placebo groups in relation to mean MMSE change, cognitive decline, or dementia occurrence.	Blood pressure lowering was associated with no harm in relation to cognitive outcomes, and the lack of a beneficial effect on cognition may be explained by the relatively short follow-up and small blood pressure differences between comparator groups.

Table 2. Continued.

Study name (publication date)	Participant characteristic	Intervention	Cognitive outcomes	Main results	Key conclusions
HYVET-COG*** (2008) [137]	• N = 3336 • Mean age = 84 ± 3 years • 60% women • Mean baseline blood pressure = 160–200/<110 mm Hg • Mean sitting SBP of 173 mm Hg and mean standing SBP of 170 mm Hg • Mean follow-up time = 2.2 years with at least 1 follow-up assessment	Slow release indapamide with the option of adding perindopril versus placebo.	After baseline and annual MMSE administration, possible cases of dementia were defined by a fall in the MMSE score to <24 points or a drop of 3 points in 1 year with diagnostic verification by expert review meeting standard diagnostic criteria (DSM-IV).	• The mean reduction in SBP favoring the active over the placebo treatment group at 2 years was 15/5.9 mm Hg. • There were 263 incident dementia cases representing 38 per 1000 patient-years in the placebo group and 33 per 1000 patient-years in the active treatment group showing no statistically significant difference (HR: 0.86, 95% CI of 0.67, 1.09).	There was a short follow-up period because the study was terminated early as there were significant results for the primary cardiovascular outcomes, however, the addition of the HYVET-COG data to a meta-analysis provided favorable results in support of blood pressure lowering to reduce the risk of incident dementia.
PRoFESS^ (2008) [138]	• N = 20,332 ischemic stroke patients • Mean age = 66 ± 8 years • 36% women • Mean blood pressure at baseline = 144 ± 17/84 ± 11 mm Hg • Follow-up time = median 2.4 years	• 2 × 2 factorial design of either aspirin 25 mg and extended-release dipyridamole 200 mg twice a day or clopidogrel 75 mg a day and either telmisartan 80 mg or placebo once daily. Telmisartan was considered to be add-on therapy. • At 1 month SBP was reduced by telmisartan by 8.3 mm Hg and with placebo by 2.9 mm Hg.	MMSE was compared at 4 weeks after randomization and at the penultimate visit.	In relation to key cognitive outcomes among the various treatment groups, there was no significant difference in the median MMSE scores, the percentage of participants with a MMSE score of 24 points or less, the percentage with a drop in MMSE score of 3 points or more between 1 month and the last study visit, or in the proportion of patients with cognitive impairment or dementia (as determined by clinical impression).	Cognitive decline in patients with ischemic stroke was not affected by telmisartan or either of the antiplatelet regimens. The lack of a significant difference may be explained by the short follow-up period and relatively small reductions in blood pressure compared to other studies.

Table 2. Continued.

Study name (publication date)	Participant characteristic	Intervention	Cognitive outcomes	Main results	Key conclusions
ONTARGET and TRANSCEND^^ (2011) [139]	• N = 25,620 in ONTARGET, and 5926 in TRANSCEND. Data from the 2 trials were pooled.	The 2 trials provide different means of blocking the renin-angiotensin system (RAS).	Secondary outcomes were cognitive impairment established by investigator impression or a score of $\leq$23 on the MMSE, and cognitive decline defined as a decrease of $\geq$3 points on the MMSE compared between a baseline and follow-up study exam.	• There were no clear beneficial effects on cognition based on the different approaches to blocking the RAS.	Although there were no clear beneficial effects of RAS blockade on cognition, persons with the lowest SBP had a greater likelihood of preservation of cognitive function though meta-regression analysis showed no clear benefits of BP lowering. Longer periods of blood pressure lowering may be necessary to achieve microcirculatory and subsequent cognitive benefit.
	• Mean age ~66 years	• In ONTARGET, 7865 were allocated to ramipril, 7797 to telmesartan, and 7807 to combination of the latter 2 drugs.			
	• 27% women in ONTARGET, and 43% women in TRANSCEND	• In TRANSCEND, 2694 were allocated to telmisartan and 2689 were allocated to placebo, in those intolerant to angiotensin converting enzyme inhibitors.		• The trials were not statistically powered to detect small treatment effects.	
	• Follow-up time = 56 months				
	• Participants had cardiovascular disease or diabetes mellitus at entry (but not heart failure)				
SPS3^^^ (2012) [140–142]	• N = 3020 patients with recent lacunar infarction, of which 2916 had baseline CASI scores	• 2 $\times$ 2 factorial design of antiplatelet therapy (aspirin versus aspirin plus clopidogrel) and blood pressure lowering therapy to a target SBP $<$130 mm Hg versus 130–149 mm Hg.	Change in the Cognitive Abilities Screening Instrument (CASI) during follow-up. The CASI measures global cognition, attention, concentration, orientation, short-term memory, long-term memory, and other cognitive domains. Other cognitive tests were also administered.	• Changes in baseline CASI z-scores during the follow-up period did not differ statistically significantly by antiplatelet or blood pressure lowering treatment groups [141].	The authors concluded that cognition was not influenced by either antiplatelet or blood pressure lowering therapies in relatively young participants, and future studies should focus on persons at higher risk of cognitive decline.
	• Mean age = 63 years	• The mean difference in systolic blood pressure was 11 mm Hg between the 2 target blood pressure groups at 1 year (138 mm Hg versus 127 mm Hg), favoring the more intensive treatment group.		• In exploratory analyses, it was found that close to 50% of the cohort of lacunar infarction patients had MCI [140], and the pattern of MCI differed between Spanish- and English-speaking participants.	
	• 37% women, 16% Black				
	• Follow-up time = median of 3 years and maximum of 5 years				

Table 2. Continued.

Study name (publication date)	Participant characteristic	Intervention	Cognitive outcomes	Main results	Key conclusions
HOPE-3*,^ (2019) [143]	• N = 2361 (1626 completed baseline and study end cognitive assessments) • Mean age = 74 years • 59% women • 45% with hypertension • Follow-up time = median 5.7 years	2 × 2 factorial design comparing candesartan/hydrochlorothiazide versus placebo and rosuvastatin versus placebo.	Digit Symbol Substitution Test (DSST), modified Montreal Cognitive Assessment (m-MoCA), and Trail Making Test. Part B at baseline and study end.	• There were no significant differences in any of the cognitive measures according to treatment group. • SBP was reduced by 6.0 mm Hg in the candesartan/hydrochlorothiazide treatment group over placebo treatment.	Neither long-term blood pressure lowering nor lipid lowering significantly influenced cognitive decline.

*SHEP: Systolic Hypertension in the Elderly Program Study; **SCOPE: Study of Cognition and Prognosis in the Elderly; ***HYVET-COG: Hypertension in the Very Elderly Trial cognitive function assessment; ^PRoFESS: Prevention Regimen for Efffectively Avoiding Second Strokes trial; ^^ONTARGET and TRANSCEND: Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpont Trial and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease trial; ^^^SPS3: Secondary Prevention of Small Subcortical Strokes trial; *,^HOPE: Heart Outcomes Prevention Evaluation.

from 27 studies) [145]. The latter findings challenge the hypothesis that RAS blockade may be more likely to preserve cognition.

In a separate meta-analysis published in 2020 of individual participant data from prospective cohort studies (n = 31,090 from 6 studies), Ding *et al.* [146] found no evidence that a specific antihypertensive medication drug class was more effective than any other in reducing the risk of dementia. In this particular analysis, the authors also concluded that those persons using a blood pressure lowering medication had a reduced risk of incident dementia (HR 0.88, 95% CI of 0.79, 0.98; $p = 0.019$) and AD (HR 0.84, 95% CI of 0.73, 0.97; $p = 0.021$) compared to those not taking blood pressure lowering medication. However, there was no association between administration of blood pressure lowering medication and incident dementia or AD in those with normal blood pressure [146].

In another publication from 2020 of 14 RCTs and 96,158 participants of which 12 addressed incidence of dementia, 8 reported decline in cognition, and 8 changes in cognitive test scores, the mean age of subjects was 69 years and approximately 42% were women [147]. At baseline, mean blood pressure was 154/83.3 mm Hg. There was a reduced risk of dementia or cognitive impairment among participants followed for a mean duration of 4.1 years and who were taking antihypertensive medication compared to controls (odds ratio 0.93, 95% CI of 0.88, 0.99; absolute risk reduction 0.39%). In addition, there was a reduction of cognitive decline (odds ratio 0.93, 95% CI of 0.88, 0.99; absolute risk reduction 0.71%), but blood pressure lowering had no beneficial effect on cognitive test scores.

Limitations of some of the above methodologies should be noted. Sub-group and meta-regression analyses from systematic reviews may be prone to ecological bias, and use of RCT data rather than observational data may be better suited to resolve some of the challenging and unanswered questions of interest.

5. Is blood pressure lowering alone sufficient to maintain cognition?

Given that many persons who are at risk for cognitive impairment and dementia are older and have multiple cardiovascular risks, it may be reasonable to conclude that reduction of blood pressure alone may not be sufficient to reduce the risk of cognitive impairment and dementia as it may require a multi-domain approach of management of multiple risks. A recent wave of studies has answered the call for such clinical science, and the topic has been reviewed by one of us in a separate publication [148]. This is further supported by results of the recent Lancet Commission study suggesting 12 potentially modifiable risk factors for dementia: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury and air population [74]. These modifiable risk factors account for 40% of dementia cases, with a population attributable risk of 2% for hypertension alone [74]. In this context, a growing body of evidence has focused on the cumulative impact of various vascular and metabolic risk factors and their interaction on cognitive outcomes. For example, Petrova *et al.* [149] showed that those with diabetes type II and hypertension may have a greater cognitive decline than normotensive diabetic patients (n = 113, mean age of 56 years). Metabolic syndrome, its components, and exposure to a higher burden of vascular risk factors as defined by the American Heart Association/American Stroke Association (AHA/ASA) recommendations have been consistently linked with poor cognitive outcomes [1, 20, 150–153]. Therefore, a multi-domain approach for the management of modifiable vascular and metabolic risk factors could be more effective in preventing dementia and/or its progression than a single component approach such as hypertension.

Of note, one of the studies provides promise that a multi-domain approach to prevent cognitive decline in at-risk older persons in the general population may be effective [154]. The RCT of interest is FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) [154]. The trial included persons 60–77 years of age who were screened using the CAIDE (Cardiovascular Risk Factors, Aging and Dementia Risk Score) to assure high enough risk (CAIDE scores were at least 6 points and cognition was at a mean level or slightly below that expected for age). The active intervention group had targeted diet, exercise, and cognitive training, and vascular risk monitoring, whereas a control group was counseled on general health advice. The primary outcome was change in cognition according to a comprehensive neuropsychological test battery (NTB). Approximately 630 participants were recruited to each intervention group.

Over a 2-year follow-up period, there was a mean change of the NTB total z-score of 0.20 in the intervention group versus 0.16 in the control group [154]. The between group differences in the NTB scores annually was 0.022 (95% CI of 0.002, 0.042; $p = 0.030$), and there were 7% adverse events in the intervention group (5% musculoskeletal versus 0%, respectively) versus 1% in controls. Of note, in addition to beneficial effects on overall cognition, the intervention group showed significant positive effects on executive function, processing speed, and body mass index, dietary habits, and physical activity. Such an intensive interventional program may be difficult to adopt on a wider basis. A worldwide FINGERS Network study has been implemented and is currently ongoing to seek further evidence of the influence of cardiovascular risk reduction on dementia, AD and cognitive impairment prevention in different populations [155]. Of additional note, SPRINT MIND has an ongoing multi-year extension study.

Finally, when considering multi-domain interventions, one must take into account other variables such as patient frailty, multiple comorbidities, polypharmacy, life ex-

Table 3. Blood pressure treatment target considerations for maintenance of cognition.

SBP target of 120 mm Hg for patients meeting SPRINT MIND trial eligibility criteria.
For patients not meeting SPRINT MIND eligibility criteria:
SBP target of ≤130 mm Hg.
For patients not tolerant to a SBP ≤130 mm Hg, aim for a SBP target range of 130–160 mm Hg.
Potential risks (e.g., syncope, electrolyte imbalance) and benefits of intensive BP reduction to reduce cognitive, cardiovascular and stroke outcomes are to be considered.
Considerations for future BP lowering RCTs aimed at preservation of cognition:
Adequate sample size and follow-up time to ensure adequate statistical power.
Utilization of MCI and/or dementia as the primary outcome rather than individual neuropsychological tests.
Selection of patients with high enough cardiovascular risk.
Multi-domain intervention rather than a single domain intervention.

pectancy, and patient preferences, especially in relation to values in older adults.

6. Perspectives on blood pressure lowering and cognition and setting targets for blood pressure lowering to maintain cognition

Observational epidemiologic study suggests that midlife hypertension is significantly associated with cognitive impairment and dementia in later life. In contrast, the larger scale RCTs which have disparate study methodology, have not consistently shown a beneficial effect of blood pressure lowering on cognition. The RCTs, however, are informative in relation to the following key points [148]: (1) Adequate sample size and follow-up time are desirable to assure that the study is adequately statistically powered; (2) In RCTs, it may be advantageous to utilize MCI and/or dementia as the primary outcome endpoint(s) rather than individual neuropsychological test domains; (3) Selection of patients at high enough cardiovascular risk seems prudent; and (4) Multi-domain interventions may be more desirable than single domain interventions (Table 3).

The precise blood pressure lowering target to optimize cognition remains somewhat elusive. For example, the main US blood pressure guidance statement suggests that blood pressure lowering is reasonable to prevent cognitive decline and dementia but does not set a specific blood pressure lowering target [156]. The recent Lancet Commission statement recommends treatment of hypertension to a SBP target of <130 mm Hg in midlife but does not address later life blood pressure lowering targets [74]. Similarly, the US National Academies of Sciences, Engineering, and Medicine provide guidance that lowering blood pressure provides encouraging but not definitive results in relation to preventing cognitive decline and dementia but does not specify a blood pressure lowering target [157].

Based on clinical experience and recent guidance statements, and observational epidemiologic data, we provide consideration of the following blood pressure treatment targets for individual patients (Table 3): (1) For patients who meet SPRINT MIND study eligibility criteria, it may be reasonable to aim for a SBP target of 120 mm Hg [124]; (2) For other persons who can tolerate blood pressure lowering, it may be reasonable to aim for a SBP lowering target of ≤130 mm Hg (a blood pressure lowering target utilized for a number of general risk conditions according to the 2017 US guidance statement) [156]; and (3) As there are still many unknowns and challenges in relation to blood pressure lowering and maintenance of cognition which are referred to below, other persons who have difficulty lowering blood pressure or do not tolerate blood pressure lowering to the aforementioned levels, may be candidates for a SBP level range of 130–160 mm Hg. One should keep in mind that potential benefits of blood pressure lowering on reduction of cardiovascular diseases and stroke must be balanced against the risk of adverse events of blood pressure lowering such as dizziness, syncope, and other adverse events [123, 158].

7. Caveats, unknowns, and challenges to blood pressure lowering for maintenance of cognition

A number of unanswered questions, challenges, and unknowns remain in relation to blood pressure lowering to maintain cognition and serve as potential foci for additional research. The questions and individual patient clinical circumstances may lead to a higher blood pressure target in certain cases (e.g., SBP target of 130–160 mm Hg) [123, 158]: (1) Is it safe to lower blood pressure in very elderly persons [159], as a number of observational epidemiologic studies suggest a higher blood pressure may be better? (2) What should be the blood pressure strategy if there is evidence of cognitive impairment (is blood pressure lowering safe)? (3) State of the cerebral arteries: are we risking causing more brain infarcts with blood pressure lowering in some persons, in deep poorly collateralized brain areas, and can we predict who will or will not tolerate blood pressure lowering by better understanding the mechanism of underlying cerebral artery compromise? (4) What is the best strategy for diabetic patients (e.g., ACC/AHA guidance: blood pressure target: <130/80 mm Hg) [156]?

Author contributions

SM wrote sections 1, 2 and 3. FAS contributed to critical revision of manuscript for important intellectual content. PhBG wrote sections 4, 5 and 6. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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