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Perspectives on the relation of blood pressure and cognition in the elderly

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ABSTRACT

The relationship of blood pressure to cognition in the elderly is a poorly understood topic. Many questions exist such as does treatment of hypertension prevent cognitive decline, the optimal timing of intervention and selecting the appropriate agent. In this review we will explore recent epidemiologic data and clinical trials addressing hypertension and cognition, review pathophysiology of chronic hypertension and effects of brain function, discuss the timing of intervention and finally review opportunities for future research.

Introduction

Raised blood pressure is a leading cause of death and disability worldwide [1]. In the United States (US), it is estimated that more than 50% of deaths from coronary heart disease and stroke occur in persons with hypertension [1]. Because raised blood pressure has a high prevalence in the population (estimated to be 46% in the US according to a recent guidance statement [1]) and a high relative risk for stroke, it has a substantial estimated population attributable risk of 25% to 50%, meaning that 25% and up to 50% of strokes are attributed to hypertension [2]. Raised blood pressure is an ideal target for stroke and other cardiovascular prevention as there are multiple observational and clinical trials supporting blood pressure reduction for stroke and cardiovascular prevention [3].

The role of blood pressure lowering for the maintenance of cognitive vitality in the elderly, however, has been the subject of controversy [4–6]. It is less clear whether blood pressure lowering is efficacious and safe in the elderly in relation to preservation of cognitive function. Over time, concern has been raised that blood pressure lowering in the elderly could be associated with loss of cerebral autoregulation and thus, adverse outcomes including worsening of cognition. Some experts have even advocated less stringent blood pressure control (i.e., allowance of higher systolic blood pressure targets) in the elderly in relation to maintenance of cognition.

In this topical review, we discuss four key aspects of blood pressure lowering in the elderly: 1. Observational epidemiologic data and clinical trial studies that either support or refute blood pressure lowering in the elderly for preservation of cognitive vitality; 2. Underlying pathology and proposed mechanisms linking blood pressure to cognition impairment; 3. Guidance statements and controversies regarding blood pressure treatment, timing and specific interventions for possible cognitive preservation; and 4. Opportunities for future research. Based on the scope of this topical review, our discussion is limited to select studies known to the authors and available in their personal files, rather than those emanating from a formal and an exhaustive evidence-based literature review. Because we are reporting on selected studies, the information in this manuscript represents examples of concepts that we wish to emphasize and advance forward.

Definitions

Cognitive decline can be defined as decline that is greater than expected from normal aging document by validated cognitive testing over time. Mild cognitive impairment (MCI) includes cognitive decline without affecting daily activities of living. Dementia can be the diagnosis once there is enough cognitive decline to affect daily activities of living and at least 2 cognitive domains are involved. Finally, Fillit et al., refers to cognitive vitality as the brain's ability to adapt and learn.

Epidemiology: impact of blood pressure on cognition

In 1999, following the occasion of a dementia harmonization conference in Osaka, Japan, a group of international expert attendees reviewed the epidemiological literature on prospects

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for prevention of vascular dementia by control of cardiovascular risks [7]. In relation to hypertension and based on a number of epidemiological observational studies such as the Honolulu–Asia aging study, Longitudinal Population Study of 70-year-old subjects in Goteborg, Sweden, a cohort of elderly men in Uppsala, Sweden, the US National Heart, Lung and Blood Institute Twin Study, and other studies, it was concluded that blood pressure elevation in midlife or later life was a prime candidate for modification to prevent cognitive decline or dementia in later life [7]. At that time, one key clinical trial, the Systolic Hypertension in Europe (Syst-Eur) trial had been published and showed that the long-acting calcium channel blocker nitrendipine reduced the incidence of dementia by about 50% when compared to placebo, and most of the cases that had been prevented were Alzheimer disease (AD) ones [8].

To further expand on the Syst-Eur trial, eligibility included individuals who were at least 60 years of age without dementia (based on having a MMSE of greater than 23) and a SBP of 160–219 mm Hg, with DBP below 95 mm Hg. Individuals were randomized into treatment with nitrendipine, with the possible addition of enalapril maleate, hydrochlorothiazide, or both vs. placebo. The diagnosis of dementia was established if the MMSE score was 23 or less during follow up screening and dementia criteria were met per DSM-III-R. Vascular dementia was differentiated from degenerative disease based on using the modified ischemic score. At a median follow-up of 3.9 years, long-term antihypertensive therapy reduced the risk of dementia by 55% (43 vs. 21 cases, $P < .001$) compared to the control arm of the study [8]. Of the 22 cases in which dementia was prevented, 17 were of Alzheimer disease (AD). In addition, it was concluded that vascular risks were common and modifiable and provided a means whereby vascular dementia and possibly AD could be postponed or prevented [7].

During the next fifteen years, the hypothesis of whether blood pressure lowering was efficacious or effective and safe was studied in additional observational epidemiological studies and clinical trials. Now, we review key evidence-based summary articles addressing the issue of blood pressure lowering and maintenance of cognitive vitality.

Institute of Medicine (IOM) Report (2015) [9]. The IOM study report focused on public health aspects of cognitive aging to better understand the brain, cognition and aging [9]. A portion of the report included an assessment of risks and protective factors and interventions for cognitive vitality. The authors of the report emphasized that hypertension was present in about 65% of persons 60 years of age or older and was an important preventable risk factor for cognitive decline and dementia increasing the hazard ratio to 1.24 or 1.59 for cognitive problems. According to this report, the strength of the recommendation to manage hypertension to prevent cognitive decline or dementia was based on the strength of observational studies as clinical trials were not consistent in relation to a benefit of lowering blood pressure as only some showed benefit. Studies such as Action on Diabetes and Vascular Disease: PreterAx and DiamicroN-MR Controlled Evaluation (ADVANCE), Hypertension in the Very Elderly Trial-Cognition (HYVET-COG), and Study of Cognition and Prognosis in the Elderly (SCOPE) were reviewed [9].

The authors acknowledged limitations to the available study database and need for additional study information including the potential importance of class of antihypertensive medication, timing and duration of treatment, and type of underlying cognitive impairment with the contention that AD may not respond to blood pressure lowering therapy [9]. In addition, the authors emphasized the importance of blood pressure control for prevention of heart disease and stroke as a fundamental rationale for blood pressure lowering. Finally, it was concluded in the IOM report that it was useful to take action to reduce and manage hypertension in an attempt to prevent cognitive decline with aging [9].

Report of the National Academies of Sciences, Engineering, Medicine (NASEM) (2017) [10]. The NASEM report focused on the state of knowledge about what interventions may be effective to prevent or slow cognitive decline and dementia [10]. In this report, randomized controlled trials were emphasized in the final clinical decision making recommendations. Similar to the IOM report [9], the NASEM report emphasized the importance of blood pressure lowering in relation to reduction of heart attack and stroke [10]. In a discussion of class of blood pressure lowering medication, it was concluded that there was insufficient evidence to conclude that one class of blood pressure lowering agent was superior to another such class for prevention of cognitive decline or dementia [10].

In the NASEM report, the following key systematic review findings were noted: 1. Among hypertensive populations, there was generally *low-strength evidence* that anti-hypertensive treatment versus placebo had benefit on cognitive performance in adults with normal cognition at baseline; 2. There was *moderate-strength evidence* that angiotensin converting enzyme inhibitor plus thiazide diuretic therapy versus placebo and angiotensin receptor blocker medication versus placebo had benefit as assessed by brief cognitive screening tests; 3. There was *low-strength evidence* of no benefit on cognition of intensive versus standard antihypertensive control or any fixed blood pressure lowering treatment versus another; 4. In relation to stepped multiple agent blood pressure lowering, one trial demonstrated a positive effect and three trials showed no effect; and 5. Of 2 trials that showed subgroup data, cognition studied by age or other baseline characteristics was unremarkable, and thus did not show a target subgroup that might benefit from such therapy [10]. The review also included a discussion of the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial that showed no clinical benefit on cognitive performance of intensive blood pressure lowering over standard therapy in persons with type-2 diabetes mellitus [11].

The authors of the NASEM report referred to a number of limitations of the existent clinical trial database including but not limited to potential heterogeneity of effect (e.g., by age), the occurrence of underpowered secondary analyses, less than optimal cognitive assessments in some studies, short duration of follow-up, and other factors [10]. After assessing the role of blood pressure lowering therapy against Bradford Hill criteria for causation, the authors arrived at the following conclusions in relation to blood pressure lowering and cognition: 1. Observational studies supported blood pressure management as a factor that reduced the risk of dementia and was consistent with a causal relationship; and 2. Although randomized controlled trial data were inconsistent, observational study results supported treatment of blood pressure and like physical activity, blood pressure lowering was broadly recommended for primary, secondary, and tertiary prevention of many chronic conditions [10]. The beneficial blood pressure lowering effect on maintenance of cognitive vitality might especially be pertinent when applied in midlife [10]. Finally, it was concluded that the blood pressure management for persons with hypertension was an *encouraging but inconclusive* means to prevent, delay or slow AD.

Recent American Heart Association (AHA)/American Stroke Association (ASA) Guidance Statements on Hypertension and Cognition. In relation to hypertension and cognition, recent AHA/ASA guidance statements make several salient points: 1. Raised blood pressure leads to disruption of brain blood vessel structure and function and ischemic damage of brain white matter critical to cognition, may have its greatest influence on cognitive change in later life and in midlife, and in addition, hypertension may promote AD [12]; Nor-

Table 1
American Heart Association/American Stroke Association life's simple 7 to define ideal brain health in adults [3].

Factor	Definition
1. Hypertension	Untreated blood pressure <120/80 mm Hg
2. Fasting blood glucose	<100 mg/dL
3. Untreated total cholesterol	<200 mg/dL
4. Smoking status	Nonsmoker
5. Physical activity	Moderate-intensity activity > 150 min/week or vigorous intensity activity > 75 min/week or combination
6. Body mass index	<25 kg/m^2
7. Diet	Fruits and vegetables: ≥ 4.5 cups/day; 2. Fish: ≥ two 3.5-oz servings/week (preferably oily fish); 3. Fiber-rich whole grains (≥ 1.1 g of fiber per10 gram of carbohydrate): ≥ three 1-oz-equivalent servings/day; 4. Sodium: < 1500 mg/day; 5. Sugar-sweetened beverages: ≤ 450 kcal (36 oz)/week

mal untreated blood pressure is a component of AHA's Life's Simple 7 (Table 1) and as such serves in part to define optimal brain health in adults [3]; and 3. Persons at risk of vascular cognitive impairment should receive blood pressure lowering therapy [1,4].

In addition, in an AHA/ASA scientific statement on prevention of stroke in patients with silent cerebrovascular disease, the potential importance of vascular risks including hypertension is emphasized as is the association between silent stroke manifestations and risk of cognitive impairment [13].

Beyond AHA's Life's Simple 7, the *Institute of Medicine (IOM) Report (2015)* [9] recommends to take actions that may promote cognitive health including obtaining adequate sleep and treating underlying sleep disorders if needed. The IOM report also stresses the importance of being socially and intellectually engaged while maintaining lifelong learning.

Multi-domain Treatment Trials. The observation that a greater number of healthy lifestyle behaviors and fewer cardiovascular risks (see Table 1 on AHA's Life's Simple 7) is associated with preservation of cognitive vitality has led to multi-modal treatment trials designed to assess the hypothesis that practice of healthy cardiovascular lifestyles and control of cardiovascular risk factors including hypertension may result in preservation of cognitive function [3]. A discussion of these trials is beyond the scope of this topical review but are summarized elsewhere [14]. A key take-away message is that focus on control of only one factor such as hypertension may not be sufficient to successfully achieve cognitive preservation as one ages. Control of multiple risks may be necessary. One such study, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), has provided proof-of-concept that a multi-domain strategy of diet, exercise, cognitive training, and vascular risk monitoring and control may improve cognitive function when compared to a control group that received only general health advice [15]. Whereas multi-domain trials provide important insights into the prevention of dementia or cognitive decline, a limitation is that they do not provide a specific answer to the question of blood pressure management alone for prevention of dementia or cognitive impairment.

The reader is referred to Gorelick PB et al. Defining Optimal Brain Health in Adults, Table 2 for a summary of trial data on maintenance of cognitive function [3].

Pathophysiology and mechanism of hypertensive induced cognitive impairment

The pathophysiology responsible for hypertensive induced cognitive decline is complicated and diverse. There is likely a synergistic effect of multiple mechanisms that ultimately lead to white matter disease, cerebral microbleeds, brain atrophy, deposition of pathologic proteins, and ischemic stroke, all of which negatively affect cognition. The mechanisms behind hypertensive induced cognitive impairment can be divided into two broad categories; those in which hypertension *directly* plays a role in disrupting the neurovascular unit leading to stroke and *indirectly* via loss of cerebral autoregulation, neurovascular coupling, accumulation of beta amyloid, and microvascular rarefaction. In 2016, in a statement from the American Heart Association Costantino Iadecola et al., provided a detailed review of the pathophysiology involved in hypertensive induced cognitive impairment; a summary of key points follows below [12].

Direct mechanisms of hypertensive induced cognitive impairment: atherosclerosis, lipohyalinosis, disruption of blood brain barrier, and oxidative stress

Chronic hypertension leads to negative sequela for both large and small vessels. Large vessels are affected via atherosclerosis as hypertension is a well-known risk factor for development of fatty intimal plaques leading to vessel narrowing. Proliferation of the vascular smooth muscle layer in the setting of elevated blood pressure also leads to reduction in luminal diameter [16,17]. Decrease in vascular compliance occurs as a result of increase deposition of collagen, elastin and fibronectin in vessel walls [18]. Lipohyalinosis is responsible for small vessel pathology with hypertension being its main risk factor [19]. In the setting of lipohyalinosis vessel walls contain fibro-hyaline material causing an increase in arteriole stiffness, reduction in luminal diameter, and wall friability leading to hemorrhage, if the weakened vessel wall ruptures or ischemic stroke, if there is occlusion of the vessel wall lumen.

Hypertension can lead to the direct disruption of the integrity of the blood brain barrier (BBB). The BBB is vital to maintain normal cell homeostasis serving as a conduit to allow transportation of nutrients and electrolytes into and out of the cell. The loss of the BBB is associated with white matter disease and may serve as an early marker for small vessel pathology [20]. Although the precise mechanism behind the destruction of white matter is not known, it is thought to be related to perivascular inflammation through the leakage of reactive oxygen species as well as microvascular thrombi [21]. Oxidative stress has recently gained traction as a significant contributor to cognitive impairment in vascular dementia [21] with angiotensin II serving as a key contributor to the production of toxic free radical species. Angiotensin II activation leads to the stimulation of NADPH oxidase which results in vascular oxidative damage via superoxide production [17]. In the animal model (mouse), behavioral deficits have been demonstrated with angiotensin II infusions resulting in reduced cerebral blood flow and a pro-inflammatory cascade including an in increase in leukocyte adhesion, superoxide-mediated oxidative stress, BBB dysfunction, and amyloid accumulation [22,23]. Angiotensin II has also been implicated in large vessel pathology via vascular remodeling and arterial stiffening [17].

Table 2
A practical approach to blood pressure management in patients at risk for cognitive impairment [1,4–6].

1. **Overall Benefit of Blood Pressure Lowering in General:** Treatment of raised blood pressure reduces the risk of stroke, coronary heart disease and other cardiovascular disorders.
2. **Blood Pressure Lowering in Relation to Maintenance of Cognition:** It is reasonable to treat raised blood pressure to attempt to prevent dementia and cognitive decline.
3. **Blood Pressure Lowering and Class of Antihypertensive Agent:** Although angiotensin converting enzyme inhibitors (ACE-Is), calcium channel blockers and other classes of antihypertensive agents have been hypothesized to be blood pressure lowering agents of choice for maintenance of cognitive vitality, currently there is no consistent evidence that such is the case. Therefore, any of the major classes of blood pressure lowering agents may be used until there is further evidence to favor one class of blood pressure lowering agent over others. One should keep in mind that there is evidence that nitrendipine more generally or perindopril with or without diuretic therapy (indapamide) specifically, administered to stroke patients, may be beneficial.

Blood Pressure Lowering and Blood Pressure Targets for Maintenance of Cognitive Vitality: Blood pressure targets for maintenance of cognitive vitality have not been well established. Therefore, it is reasonable to aim for guidance-based blood pressure lowering targets (e.g., <130/80 mm Hg for the general population, <140/90 mm Hg for persons with a history of stroke or <130 mm Hg SBP if there has been a lacunar brain infarction). One must keep in mind that older persons may not tolerate substantial lowering of blood pressure as they may have impairment of cerebral autoregulatory capacity, and thus, the SBP lowering targets for this group may need to be adjusted on a case-by-case basis and according to tolerance (i.e., occurrence of adverse symptoms or events) to blood pressure lowering therapy.

Indirect mechanisms of hypertensive induced cognitive impairment: rarefaction, neurovascular coupling, loss of cerebral autoregulation, and amyloid deposits

Cardiovascular risk factors including chronic hypertension, yield a reduction in cerebral microvascular circulation in a process known as microvascular rarefaction [24]. Reduction of collateral vessels imposes a greater risk of ischemia leading to cognitive decline. Hypertension also indirectly leads to cognitive impairment through a loss of neurovascular coupling [21,25]. Neurovascular coupling is a normal physiologic response which results in increasing cerebral blood flow in certain areas of the brain during times of increased metabolic demand. In the setting of chronic hypertension and reduced basal cerebral blood flow, cerebral perfusion cannot accommodate to increasing metabolic demands resulting in a perfusion mismatch and cognitive decline [21,25]. Cerebral autoregulation is crucial for maintaining an adequate cerebral blood flow over a wide array of mean arterial pressures. Cerebral autoregulation is likely accomplished via vessel caliber changes which are mediated by interplay between myogenic and metabolic mechanisms [26]. In chronic hypertension there is a rightward shift in the cerebral autoregulation curve that results in higher relative blood pressure required to maintain the same cerebral perfusion [27]. This rightward shift creates vulnerability in the setting of hypotension leading to ischemia, and in the setting of sustained hypertension or rightward shift of the autoregulatory curve there is increased risk of brain hemorrhage. Finally, hypertension has also been indirectly linked to AD through the development of intracranial atherosclerosis leading to hypoperfusion and possibly other mechanisms. Hypoperfusion has been postulated to lead to an increase in beta amyloid accumulation through decrease in beta amyloid clearance as well as increase in amyloid accumulation through activation of beta secretase [28]. Furthermore, brains of persons with hypertension may be atrophic and contain more AD neuropathology than control brains.

Longitudinal effects of hypertension on cognitive decline and treatment of cognitive decline by blood pressure control

In this section we will discuss the longitudinal relationship between hypertension and cognitive decline in various age groups. We will also review the effect of blood pressure lowering to prevent cognitive decline. Finally, we will examine the effect of different antihypertensive drug classes on cognitive decline.

Multiple studies have demonstrated a longitudinal correlation between midlife hypertension (defined as 40–64 years of age) and cognitive decline in later life. For example, in the Framingham study, individuals with high systolic blood pressure (SBP) and diastolic blood pressure (DBP) in midlife had poorer performance on global cognitive scores, attention, and memory testing [29]. A similar effect was seen in the Honolulu–Asia Aging study, in which mid age participants with SBP greater than 160 had a 2-fold increase in risk of poorer global cognitive function when measured 25 years later [30]. A review of longitudinal studies indicate that late life (defined as 65–84 years of age) hypertension and the development of cognitive impairment is a less clear association [12]. Some studies have demonstrated a linear association, whereas others have demonstrated a U shaped association, and still others have not demonstrated any association [12]. The unclear relationship between late life hypertension and cognitive decline may be related to the role hypertension plays in maintaining cerebral perfusion in older patients. Hypertension in the setting of dysfunctional cerebral autoregulation and atherosclerosis seen in late life patients may ensure adequate perfusion of vital cognitive brain centers and thus, possibly preserve major cognitive domains.

This concept was recently explored in an observational longitudinal study by Mcgrath and colleagues [31] that examined the association of blood pressure from mid to late life and risk of dementia. Individuals were screened for cognitive decline based on changes in Mini-Mental State Examination (MMSE) or if concern of cognitive impairment was raised by participants or family members. Dementia was diagnosed based on DSM-IV criteria and adjudicated by a committee with at least 1 neurologist and 1 neuro-psychologist. AD was diagnosed based on criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [31]. McGrath et al. demonstrated that once again midlife hypertension (BP ≥ 140/90 mm Hg) was associated with dementia (HR 1.57, 95% [CI] 1.05–2.35), and persistence of hypertension from midlife into late life was also associated with dementia (HR 1.96, 95% CI 1.25–3.09) [31]. Interestingly, individuals who were normotensive (BP ≤ 140/90 mm Hg) in midlife and had a steep decline in SBP during mid to late life had a > 2-fold increase risk of dementia (HR 2.40, 9% CI 1.39–4.15) [31]. A SBP decline, has also been linked to an increase risk of AD if occurring within 3 to 6 years preceding the diagnosis of dementia [32].

Hypertension remains the most important modifiable risk factor in the prevention of stroke. Stroke can lead to significant morbidity, including cognitive decline. With the reduction of cardiovascular risk factors including hypertension there has been a reduction in the incidence of stroke. Therefore, it would seem that the treatment of hypertension should lead to a reduction in the incidence of cognitive dysfunction and dementia. Unfortunately, randomized controlled studies investigating the effects of controlling hypertension have not demonstrated consistent improvement in cognition or the prevention of cognitive decline/dementia [3,12].

The PROGRESS trial [33], a randomized controlled trial (RCT) which examined the effect of an angiotensin converting enzyme (ACE) inhibitor, perindopril, with or without indapamide vs. placebo in prevention of cardiovascular outcomes including stroke, did demonstrate a significant reduction in the rates of dementia (34%) ($P = .03$) and cognitive decline (45%) ($p < .001$); however, this was only seen in persons with recurrent stroke [33]. Therefore, only one RCT, the SyST-Eur trial [8], demonstrated a benefit in which antihypertensive medication lowered the incidence of dementia outside of stroke patients. The SyST-Eur trial enrolled patients who were at least 60 years old, and who had a SBP of at least 160 and a DBP of below 95 mm Hg at the time of enrollment. Treatment with nitrendipine with or without enalapril with or without hydrochlorothiazide to reduce SBP by at least 20 mm Hg to reach SBP < 150 mm Hg, resulted in 50% reduction in the incidence of dementia ($P = .05$) [8]. The remainder of RCTs demonstrated no beneficial effect of treatment on cognition [3,12].

Fittingly, a pooled meta-analysis from 2011 did not demonstrate any benefit in 8 RCTs of blood pressure-lowering therapies for the prevention of dementia [34]. However, Staessen et al. suggested that in a subgroup analysis significant benefit could be achieved if therapy involved the use of a diuretic or dihydropyridine calcium channel blocker, whereas this was not the case in a trial of renin system inhibitors [34]. Potentially, calcium channel blockers may have a neuro-protective role inhibiting inward calcium influx and subsequent apoptosis and cell death. However, it is unclear if the effect on reduction of dementia was related to a neuro-protective property of the calcium channel blocker or diuretic, or was a direct effect of blood pressure lowering.

There is some uncertainty as to the timing of hypertension treatment during one's life as it relates to cognitive outcomes. The health care provider must take into account factors such as patient age, comorbidities, and genetic risks. As previously mentioned and based on observational epidemiological studies, treatment of midlife hypertension may be beneficial as antihypertensive medications have been shown to reduce cardiovascular and cognitive risk. At either end of the age continuum, the decision to intervene becomes more complicated. In children and adolescents, prospective cohort studies have demonstrated hypertension and vascular risk factors leading to the presence of subclinical atherosclerotic lesions detected at childhood autopsies [35,36]. However, there has been significant concern regarding the long term effects of early pharmacologic intervention in children. Therefore and initially if there is no compelling rationale for pharmacologic treatment, we recommend behavioral and lifestyle modifications with close clinical follow up. Readers are referred to a guidance statement found elsewhere for treatment of blood pressure in children and adolescents [37].

For individuals 80 years of age or greater, the usefulness of lowering BP to preserve cognition is unclear [4]. Elevated blood pressure in this older population potentially plays a protective role in maintaining adequate cerebral perfusion. Also, elderly individuals with labile blood pressure are sensitive to iatrogenic causes of hypotension that could predispose to hypotension, hypoperfusion, and consequent watershed territory ischemic infarction. However, recently the SPRINT trial challenged the latter notion. The SPRINT trial enrolled hypertensive patients without diabetes to an intensive blood pressure intervention with a target SBP of less than 120 mm Hg versus standard treatment with a SBP goal of less than 140 mm Hg [38]. The results of this trial demonstrated a significant reduction (hazard ratio of 0.75; 95% confidence interval [CI], 0.64 to 0.89; $P < .001$) in the rates of adverse cardiovascular outcomes favoring the intensive treatment group compared to the standard group [38]. Reduction of adverse cardiovascular outcomes and death was consistent across prespecified subgroups, including individuals 75 years of age and older [38]. These findings raise the question whether reducing SBP to less than 120 mm Hg will help prevent dementia and reduce cognitive decline, even in late life. A sub-analysis of the SPRINT trial, SPRINT-MIND will attempt to answer this question by examining whether intensive blood pressure lowering reduces the incidence of dementia, slow decline in cognitive function, and results in less MRI- based cerebral small vessel disease compared to standard therapy. SPRINT-MIND results are expected to be published in 2019. Pending the results of the latter study, we are recommending treatment of elevated blood pressure for preservation of cognitive vitality according to prior guidance statements [1,4–6]. The American Society of Hypertension (ASH) and International Society of Hypertension (ISH) guidelines suggest for those 80 years and older, the threshold for initiating blood pressure therapy is 150/90 mm Hg or greater [39]. Caution is advised in this age population, especially in the setting of established cognitive impairment as higher blood pressure could be associated with better cognitive outcomes. Table 2 provides general guidance for blood pressure management for maintenance of cognition.

In 2017, the American College of Cardiology/American Heart Association released guidelines for the prevention, detection, evaluation and management of high blood pressure in adults. These guidelines redefined hypertension as BP of 130/80 mm Hg or higher [1]. Also, recommendations were made regarding treatment of hypertension to prevent cognitive decline and dementia. Class IIa (moderate) recommendations with a level of evidence B-R (moderate evidence with 1 or more RCTs) stated: "in adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia [1]." These guideline recommendations were based largely on the results of Syst-Eur and PROGRESS trials and the observation that no randomized controlled trial has demonstrated adverse effects on the incidence of dementia or cognitive decline. Potential pitfalls, however, include failing to address the timing of intervention and potential consequences of causing iatrogenic hypotension in elderly patients.

Measures of cognitive impairment

Evaluating the effect hypertension plays in cognitive impairment requires effective screening examinations and tests that evaluate multiple cognitive domains such as executive function, memory, language, visuospatial, and behavioral domains. Several difficulties arise when attempting to measure this effect, including estimating pre-existent cognitive impairment. The Informant Questionnaire on Cognitive Decline in Elderly (IQCODE) can be used to assess for pre-stroke cognitive decline [43]. Another potential challenge requires the examiner to distinguish between the effects of vascular cognitive impairment from concurrent neurodegenerative processes such as Alzheimer's dementia. A distinguishing factor may lie in executive domain testing. Timed test of executive functioning are especially sensitive to cognitive deficits in individuals with suspect vascular cognitive impairment [44]. When examining RCTs assessing the effects of HTN on cognition few trials performed a full battery of neuropsychological testing. Many of the RCTs used the Mini-Mental State Examination (MMSE) to determine effect on cognitive outcomes. Although the MMSE has been used as a screening tool to detect dementia, it may have a ceiling effect when attempting to screen for mild cognitive impairment. Pendlebury et al., demonstrated prospectively that only MMSE scores of > 29 had sensitivities for MCI of greater than 70% whereas MMSE < 27 had sensitivities of only 50% [45] when compared to neuropsychological battery ≥ 1 year after stroke or TIA. Therefore cases of MCI may be been overlooked when examining cognitive outcomes in multiple RCTs.

Furthermore, using the Montreal Cognitive Assessment (MoCA) may be preferred when compared to MMSE as a screening tool

Table 3
Unanswered HTN and cognition questions and keys to future research design.

Unanswered Key Question	Research Suggestion
1. What is the most appropriate time window of intervention for the management of hypertension to prevent cognitive decline?	1. Designing prospective RCTs which include multiple different age groups including individuals less than age 55.
2. What BP goal should be targeted to prevent cognitive decline and does this goal vary by age?	2. Designing prospective RCTs which have pre-specified BP target ranges. Subgroup analysis may help identify appropriate target BP ranges and if these ranges vary by age.
3. Can biomarkers which predict cognitive decline, be used to select patients who would benefit from premorbid intervention?	3. Enrolling individuals with predefined biomarkers into RCTs.
4. Does a singular (i.e., one size fits all approach) suffice? Or do therapies need to be tailored based on individual gender, age, and genetic make-up.	4. In the future, genetic sequencing may allow for precise treatment plans which will be specific to that individual patient.

to detect vascular cognitive impairment following acute stroke. YanHong Dong et al., compared the 2 test within 14 days of acute stroke in 100 patients [46]. Cutoff scores of MMSE $\leq$ 24 and MoCA $\leq$ 21 were used to define moderate-severe cognitive impairment. Of the 57 patients with unremarkable MMSE scores, 18 (32%) had abnormal MoCA scores [46]. By comparison, only 2 out of the 41 (4.9%) patients with abnormal MoCA scores had abnormal MMSE scores [46]. The authors attribute this difference to poor sensitivity of the MMSE in detection of vascular cognitive impairment, specifically in the visuospatial, executive, and abstract reasoning domains [46]. When compared with the MoCA, the MMSE subtest of Attention and Delayed Recall are not as difficult tasks. For example, in testing attention MoCA contains Digit Span and Vigilance in addition to serial 7 s, which is the only attention test contained in MMSE [46].

Also, RCTs lacked standard definitions in terms of measuring and defining vascular cognitive impairment therefore making the comparison of studies difficult. In 2006, the VCI Harmonization Conference convened experts in the field to determine common standards to define the description and study of vascular cognitive impairment [47]. 3 separate protocols were developed accounting for different research needs and clinical settings: 60 minute, 30 minute, and 5 minute protocols. 4 cognitive domains were to be tested included executive/activation, language, visuospatial, and memory. Individual well-validated neuropsychological tests were selected by expert panel members within each cognitive domain category. The reader is instructed to refer to reference 47 for a list of individual test protocols. The use of common standards in defining VCI is crucial for future research and was a major flaw and oversight in previous RCTs.

Future research

Gaps remain in our knowledge regarding stroke and cognition. Several key questions will need to be addressed when moving forward. First, does treating hypertension in itself prevent or slow cognitive decline and if so when does one initiate treatment (middle age or later)? Thus far only one primary anti-hypertensive RCT, Syst-Eur trial [8], has demonstrated a lower incidence of dementia with such an intervention. One possible explanation for the propensity for lack of benefit of blood pressure lowering therapy lies in the timing of the intervention. A majority of patients enrolled in these RCTs have included patients 55 years or older. It is possible that a successful trial will entail intervening at an earlier stage before the deleterious and irreversible effects of hypertension have taken their toll. Also, modifying blood pressure solely may not be a sufficient intervention. A multimodal approach, including modification of other cardiovascular risks, diet, life style changes, and cognitive training, may be warranted. Recently, the FINGER trial demonstrated that a multi-domain intervention could be beneficial to cognitive vitality in at risk elderly individuals [15]. Unfortunately, other multimodal trials have not demonstrated significant benefit on cognition or the prevention of dementia [40,41]. Second, can we identify individuals relatively early in life who will develop cognitive decline later in life to allow us to intervene before it is too late? The combination of low beta amyloid, elevated tau and p-tau has been used to predict future cognitive decline in healthy older individuals, and thus may serve as a viable biomarker panel, though it needs to be proven if these biomarkers are enough upstream to allow maintenance of cognitive vitality [42]. Also, advances in neuroimaging, including diffusion tensor imaging, MR spectroscopy, and functional MRI may have significant value in defining vascular cognitive impairment. Finally, how do we tailor therapies and interventions to best meet the needs of patients on an individual basis? A one size fits all approach may prove to be too simplistic. With affordable and widely available genetic sequencing, personalized medical treatment may become available based on sex, age, and race-ethnicity. Table 3 includes key questions that remain unanswered and suggestions for future research designs.

Conclusion

Hypertension remains the most important modifiable risk factor in the prevention of stroke. Stroke may lead to significant cognitive decline, namely in the form of vascular cognitive impairment. Therefore it would seem logical to start treatment for the prevention of dementia or cognitive decline by prevention or treatment of raised blood pressure. The current evidence suggests that blood pressure is linked to dementia and cognitive impairment based on observational epidemiological data; however, clinical trial data have been less consistent in relation to providing results of benefit for maintenance of cognitive vitality. This may reflect premorbid vascular changes occurring over decades that lead to brain vascular injury and dysfunction and loss of cerebral autoregulation. The window of opportunity for blood pressure control to successfully maintain cognitive vitality may be in an earlier lifecycle epoch such as in midlife. Identification of biomarkers to signal the window of opportunity for such treatment are needed in our quest to prevent irreversible brain vascular and parenchymal injury leading to cognitive impairment. At the current time and including conventional gaps in our knowledge base reviewed in this text, we provide a practical approach to guide blood pressure management in patients prone to cognitive impairment and dementia (see Table 2).

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