

## Impact of Hypertension on Cognitive Function A Scientific Statement From the American Heart Association

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**Background**—Age-related dementia, most commonly caused by Alzheimer disease or cerebrovascular factors (vascular dementia), is a major public health threat. Chronic arterial hypertension is a well-established risk factor for both types of dementia, but the link between hypertension and its treatment and cognition remains poorly understood. In this scientific statement, a multidisciplinary team of experts examines the impact of hypertension on cognition to assess the state of the knowledge, to identify gaps, and to provide future directions.

**Methods**—Authors with relevant expertise were selected to contribute to this statement in accordance with the American Heart Association conflict-of-interest management policy. Panel members were assigned topics relevant to their areas of expertise, reviewed the literature, and summarized the available data.

**Results**—Hypertension disrupts the structure and function of cerebral blood vessels, leads to ischemic damage of white matter regions critical for cognitive function, and may promote Alzheimer pathology. There is strong evidence of a deleterious influence of midlife hypertension on late-life cognitive function, but the cognitive impact of late-life hypertension is less clear. Observational studies demonstrated a cumulative effect of hypertension on cerebrovascular damage, but evidence from clinical trials that antihypertensive treatment improves cognition is not conclusive.

**Conclusions**—After carefully reviewing the literature, the group concluded that there were insufficient data to make evidence-based recommendations. However, judicious treatment of hypertension, taking into account goals of care and individual characteristics (eg, age and comorbidities), seems justified to safeguard vascular health and, as a consequence, brain health. (*Hypertension*. 2016;68:e67-e94. DOI: 10.1161/HYP.0000000000000053.)

**Key Words:** AHA Scientific Statements ■ Alzheimer disease ■ biomarkers ■ blood pressure ■ clinical trials ■ neuroimaging ■ therapy ■ vascular cognitive impairment

Dementia is a progressive and typically irreversible deterioration of cognitive function that is most often seen in older adults.<sup>1</sup> Dementia is one of the most common neurological disorders, affecting an estimated 30 to 40 million people

worldwide. The number of individuals with dementia is anticipated to triple by 2050 as a result of the aging of the population, demographic shifts, and lack of disease-modifying treatments, with an associated cost exceeding \$1.1 trillion.<sup>2</sup> Alzheimer

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disease (AD) and cerebrovascular diseases are the 2 leading causes of cognitive impairment, accounting for  $\approx 80\%$  of cases and often having a mixture of both pathologies.<sup>3</sup> The term vascular cognitive impairment (VCI) indicates the entire range of cognitive deficits caused by vascular factors, whereas vascular dementia refers to the more severe cases of VCI in which the cognitive decline affects day-to-day functioning negatively.<sup>3</sup>

Among vascular risk factors, chronic arterial hypertension is a major contributor to cognitive impairment.<sup>3</sup> Hypertension, a highly prevalent disease affecting an estimated 80 million people in the United States and 1 billion individuals worldwide,<sup>4</sup> is the leading cause of global disease burden and overall health loss.<sup>5</sup> The brain is one of the main target organs affected by hypertension. Thus, excluding age, hypertension is the most important risk factor for cerebrovascular pathology leading to stroke and dementia. The harmful effects of hypertension on cognitive function have been recognized at least since the 1960s, when a study on psychomotor speed of air traffic controllers and pilots demonstrated reduced performance in individuals with hypertension.<sup>6</sup> Hypertension has been associated with reduced abstract reasoning (executive dysfunction), slowing of mental processing speed, and, less frequently, memory deficits.<sup>7</sup>

Although dementia caused by AD and vascular dementia have traditionally been considered distinct nosological entities, increasing evidence indicates that these conditions often coexist.<sup>8,9</sup> Thus, the neuropathological hallmarks of AD, amyloid plaques and neurofibrillary tangles (NFTs), are frequently associated with microcerebrovascular and macrocerebrovascular lesions in 40% to 50% of individuals with a clinical diagnosis of AD.<sup>10,11</sup> In addition, ischemic lesions markedly enhance the impact of AD pathology on cognitive function.<sup>12,13</sup> Furthermore, traditional cardiovascular risk factors have been suggested to play a role in AD,<sup>14</sup> and some estimates indicate that risk factor reduction, including treatment of hypertension, could reduce the incidence of clinically diagnosed AD up to 30%.<sup>15</sup>

Cerebral blood vessels are the main target of the deleterious effects of hypertension on the brain.<sup>16</sup> The resulting structural and functional cerebrovascular alterations underlie many of the neuropathological abnormalities responsible for the cognitive deficits, including white matter damage, microinfarcts, microbleeds, silent brain infarcts, and brain atrophy.<sup>17</sup> Hypertension is the most powerful modifiable risk factor for the cerebrovascular damage, and the dramatic reduction in stroke mortality over the past several decades has been attributed to the treatment of hypertension.<sup>18,19</sup> Surprisingly, however, the impact of hypertension and its treatment on cognitive impairment has been more difficult to assess, and several key questions remain to be answered.

Considering the growing public health import of dementia,<sup>1</sup> a critical appraisal of current knowledge of the cognitive function associated with hypertension is warranted. Although the role of vascular risk factors in cognitive impairment has been addressed in other American Heart Association statements,<sup>3</sup> there is a strong rationale for an in-depth evaluation of the specific role of hypertension. First, the effect of hypertension was previously examined in the context of several other risk factors causing vascular dementia, and a detailed analysis

of the evidence was not provided.<sup>3</sup> Second, new epidemiological data and imaging approaches have provided further insight into the relationship between hypertension and dementia and the cognitive domains that are predominantly affected. Third, the interaction between hypertension and AD pathology, a critical issue for both conditions, was not previously examined in detail. Therefore, an expert assessment is needed to update healthcare professionals on recent advances made in this field, to bring to the forefront outstanding questions, and to chart a path for future research directions.

The present statement seeks to provide an appraisal of the contribution of hypertension to age-related cognitive dysfunction. This statement refers primarily to the effects of chronic arterial hypertension. For simplicity, however, the term hypertension is used throughout the text. We first examine the effects of hypertension on the pathobiology of the cerebral circulation, focusing on the structural and functional changes induced by chronic elevations in blood pressure (BP) on the cerebral vasculature. The cognitive domains most affected by hypertension are then reviewed, highlighting their unique features and their differences from other causes of dementia. The evidence from observational studies of the effect of hypertension on cognition is presented, followed by evidence from randomized, clinical trials of BP treatment and on the cognitive effect of hypertension treatment over the life course. Subsequent sections focus on the interaction of hypertension with other risk factors and the association between hypertension and AD. The final section provides an overall summary of the evidence, identifies knowledge gaps, and provides future directions for advancing the field.

## Methods

Authors with expertise in vascular pathophysiology, epidemiology, neuroimaging, neuropathology, and cognitive science pertaining to the effects of hypertension on the brain were selected to contribute to this statement. Selection of the writing group was performed in accordance with the American Heart Association conflict-of-interest management policy. Topics for the statement were identified by the chair and co-chair and revised with input from the writing group. Subgroups of experts for each of the topics were established and charged with writing the section of the statement pertaining to their expertise. Each subgroup performed a search of the relevant English literature considered for inclusion in this statement using an up-to-date search strategy of reference databases and appropriate search terms. In addition to identifying the article reporting the main cognitive outcomes, we also reviewed, if relevant, the report on the primary outcome of the trial and on the trial design. Because of the heterogeneity of the studies spanning several decades, rigid inclusion/exclusion criteria could not generally be applied. We did not use a data abstraction tool. Conflicts were resolved by group consensus. The search also included a review of bibliographies and manual searches of key articles. Drafts of each section were written and sent to the chair and co-chair of the writing group for editing and elimination of redundancy. The edited sections were returned to the group members for clarification and revision and sent back to the chair and co-chair. The sections were then assembled in a single document that was sent back to

the members for discussion and comments. On the basis of these discussions and consensus, the sections were then edited accordingly by the primary author and returned to the chair and co-chair for further editing. The final document was circulated among all members of the writing group, and once consensus was reached, the final document was submitted for independent peer review. After peer review, the final document was approved for publication by the American Heart Association Council on Hypertension, Stroke Council, and Science Advisory and Coordinating Committee. After careful review of the available data, the group determined that there were insufficient data to make evidence-based recommendations. Therefore, specific recommendations are not provided.

### Effects of Hypertension on Cerebrovascular Structure and Function

The cerebral vasculature is the main target of the deleterious effects of hypertension on the brain. Most of the vascular alterations induced by hypertension contribute to cognitive impairment by leading to hypoperfusion, ischemic and hemorrhagic stroke, and white matter injury. This section outlines the major changes that occur in the cerebral vasculature during hypertension, focusing on the structure and function of large and small cerebral vessels, progression of atherosclerosis, and blood-brain barrier (BBB) integrity.

#### Vascular Structure

In humans as in animal models, hypertension is associated with changes in structure of the vascular wall of large, medium, and small cerebral vessels (arterioles, capillaries, and venules). At the different levels of the cerebrovascular tree, endothelial and smooth muscle cells are closely associated with brain cells (astrocytes, neurons, microglia) and perivascular cells, constituting the neurovascular unit.<sup>20</sup>

#### Atherosclerosis

Hypertension promotes atherosclerosis in both extracranial and intracranial arteries feeding the brain and accelerates the progression of intracranial atherosclerosis.<sup>21</sup> Advanced atherosclerotic lesions impair blood flow and are a major site of thrombogenesis.

#### Vascular Remodeling and Stiffening

Hypertrophic remodeling consists of hypertrophy of smooth muscle cells resulting in an increased cross-sectional area of the arterial or arteriolar wall and a reduction in the vessel lumen.<sup>22,23</sup> Inward remodeling is a rearrangement of the vessel wall that results in a reduction in lumen diameter.<sup>24</sup> Both forms of remodeling are seen in cerebral arteries and arterioles in experimental models of hypertension, with supporting evidence in human hypertension as well.<sup>23–25</sup> Chronic hypertension also induces deposition of collagen and fibronectin and elastin fragmentation of the vessel wall, leading to increased stiffness of large cerebral arteries.<sup>26</sup> In smaller arterioles, as a result of disruption of the BBB (see Blood-Brain Barrier below), an inflammatory reaction may ensue that is associated with the production of reactive oxygen species and protease upregulation.<sup>27</sup> Clinical measures of aortic and large-artery stiffening are good predictors of cerebrovascular events and VCI.<sup>28–30</sup>

#### Small-Vessel Disease

Hypertension causes typical alterations in small arteries and arterioles supplying the subcortical and basal ganglia white matter, resulting in small-vessel disease (SVD), a major cause of lacunar strokes and cerebral hemispheric white matter damage.<sup>17</sup> These subcortical vessels might be more vulnerable to the mechanical stresses caused by hypertension because of their short linear path from larger vessels at the base of the brain.<sup>16,31</sup> The typical pathological substrate of hypertensive SVD is arteriolosclerosis,<sup>17</sup> which is characterized by loss of smooth muscle cells, deposits of fibro-hyaline material, narrowing of the lumen, and thickening of the vessel wall (lipohyalinosis). In more advanced cases, fibrinoid necrosis of the vessel wall results in vessel rupture and hemorrhage (intracerebral hemorrhage and microbleeds).

#### Microvascular Rarefaction

Loss of microvessels occurs in hypertension and during aging.<sup>32,33</sup> Such changes, in concert with vascular remodeling and stiffening, are thought to contribute to the progressive reduction in resting cerebral blood flow (CBF) associated with hypertension.<sup>34–36</sup> Rarefaction may also reduce the potential for a compensatory collateral circulation in conditions of vascular insufficiency or occlusion.

#### Mechanisms

The renin-angiotensin-aldosterone system and angiotensin II are key determinants of structural changes during hypertension. The renin-angiotensin-aldosterone system is a major therapeutic target in patients with essential or primary hypertension,<sup>37</sup> but the mechanisms of renin-angiotensin-aldosterone system activation remain to be established. Whereas increases in circulating angiotensin II occur in renovascular and obesity-associated hypertension,<sup>38</sup> plasma angiotensin II is not elevated in the majority of patients with essential hypertension.<sup>39</sup> Rather, local angiotensin II production and signaling in brain, vessels, and other tissues may drive hypertension and the associated vascular changes.<sup>37,40</sup>

Angiotensin II has also been implicated in plaque composition and instability, which may underlie the effects of hypertension on atherosclerosis progression.<sup>41,42</sup> Interestingly, intracranial atherosclerosis has also been linked to AD. It has been postulated that the hypoperfusion caused by arterial stenosis may lead to reduced amyloid- $\beta$  (A $\beta$ ) clearance and increased A $\beta$  production by activating  $\beta$ -secretase, a protease involved in A $\beta$  cleavage from the amyloid precursor protein.<sup>43</sup> In turn, A $\beta$  can promote atherosclerosis by inducing inflammation, endothelial dysfunction, and oxidative stress.<sup>20,43</sup> Angiotensin II can also promote A $\beta$  cleavage from amyloid precursor protein by activating  $\beta$ - and  $\gamma$ -secretase and aggravate the vascular dysfunction induced by A $\beta$ .<sup>44,45</sup>

Angiotensin II can induce inward and hypertrophic remodeling and vascular stiffening.<sup>22</sup> Remodeling is mediated by free radicals produced by the enzyme NADPH oxidase and hypertrophy by activation of epidermal growth factor receptor probably resulting from mechanical stress and other mechanisms.<sup>46,47</sup> Mechanisms of large-artery stiffening may also include mechanical stress leading to activation of p38 mitogen-activated protein kinase and T-cell-mediated interleukin-17 production.<sup>48</sup> The factors mediating rarefaction have

not been elucidated, but vascular oxidative stress may suppress the production and action of trophic factors, resulting in vascular atrophy.<sup>27</sup> In addition, loss of endothelial nitric oxide synthase-derived nitric oxide may also be a factor in microvascular rarefaction.<sup>32,33</sup> Aging and hypertension may act in an additive fashion because hypertension causes premature rarefaction with aging.<sup>32</sup> The mechanisms of hypertension-induced SVD are thought to be diverse and may include endothelial dysfunction, BBB alterations leading to extravasation of plasma proteins, vascular inflammation, and microthrombi (Blood-Brain Barrier section).

### Vascular Function

Chronic hypertension exerts profound effects on cerebrovascular function, disrupting major factors regulating the cerebral circulation. These include endothelium-dependent mechanisms, neurovascular coupling, and autoregulation.

#### *Endothelium-Dependent Mechanisms*

Endothelial cells are a major determinant of vascular tone. By the release of vasoactive factors such as nitric oxide and prostanoids, along with endothelium-dependent hyperpolarization, these cells influence the contractile state of smooth muscle and regulate CBF in response to neurochemical, metabolic, and mechanical signals (shear stress acting on the vessel lumen).<sup>49–51</sup> Therefore, endothelial cells are critical in regulating the distribution of microvascular flow at the local level.<sup>22,52</sup> In addition, the endothelium protects vessels against thrombosis, atherogenesis, and formation of vascular A $\beta$  deposits in AD.<sup>22,49</sup> Hypertension disrupts endothelial cell function, leading to a reduction of the ability of endothelial cells to regulate microvascular flow and to exert their antithrombotic and antiatherogenic effects.<sup>22</sup> Thus, changes in endothelial function may play a role in the effects of hypertension in reducing resting CBF and promoting atherosclerosis and A $\beta$  accumulation and have been associated with stroke, VCI, white matter disease, and AD.<sup>53–56</sup>

#### *Neurovascular Coupling*

Increases in cellular activity in the brain require proportional increases in blood flow, often called neurovascular coupling or functional hyperemia.<sup>27,57</sup> Neurovascular coupling ensures adequate delivery of oxygen, glucose, and other nutrients during cellular activation, along with removal of metabolic byproducts. In response to neural activation, neurons and glia produce signals that communicate with vascular cells, resulting in increases in blood flow highly restricted to the activated areas.<sup>27,57</sup> In experimental models as in humans, hypertension attenuates the increase in CBF induced by neural activity.<sup>16,58</sup> The resulting mismatch between energy demands and blood flow delivery, along with reduced basal CBF, is thought to contribute to the cognitive decline induced by hypertension.<sup>16,27</sup>

#### *Autoregulation*

In humans as in animals, CBF remains relatively constant over a wide range of mean arterial pressures (perfusion pressures;  $\approx$ 60–150 mmHg),<sup>50,59,60</sup> a property of the cerebral circulation called autoregulation. Cerebral autoregulation depends on the intrinsic ability of vascular muscle to constrict when

transmural pressure increases (myogenic tone and reactivity) and to relax when transmural pressure decreases. Hypertension leads to a right shift of the relationship between BP and CBF (autoregulation curve), so that the same level of cerebral perfusion occurs at higher levels of BP.<sup>61</sup> This shift protects the cerebral circulation from the damaging effects of high BP but can also cause ischemic brain injury if sudden or large reductions in BP occur. Even in normotensive individuals, sudden large rises in arterial pressure can overwhelm autoregulatory mechanisms, resulting in massive CBF increases, BBB damage, and cerebral edema, as observed in hypertensive encephalopathy and the posterior reversible encephalopathy syndrome.<sup>62–64</sup> In turn, acute hypotension leads to decreases in CBF, causing “watershed” infarcts in border zones between adjacent arterial territories.<sup>27,50</sup>

#### *Mechanisms*

Hypertension-induced vascular oxidative stress has been implicated in the alterations in endothelium-dependent responses and functional hyperemia. In models of angiotensin II-dependent hypertension, NADPH oxidase is a major source of oxidative stress,<sup>16</sup> but the cells producing the radicals at the vascular level have not been identified. Evidence of oxidative stress has been reported in the brain of individuals with SVD and white matter damage.<sup>65</sup> The mechanisms of the shift of autoregulation may involve hypertension-induced changes in myogenic responses and mechanical consequences of vascular remodeling and stiffening.<sup>16</sup> The shift in autoregulation is especially damaging to the periventricular white matter, which is supplied by terminal branches arising from separate arterial territories and thus is most susceptible to hypoperfusion.<sup>66,67</sup> Accordingly, the severity of white matter injury correlates with the magnitude of autoregulatory dysfunction.<sup>68</sup> In genetic models of hypertension, there is evidence that increased myogenic tone, endothelial dysfunction, and inward remodeling can be prevented with pharmacological targeting of the renin-angiotensin-aldosterone system.<sup>69</sup> However, much less is known about the extent to which hypertension-induced vascular changes are reversible. Further work is needed to determine which cerebrovascular end points that are affected by hypertension are also reversible and amenable to treatment.

### Blood-Brain Barrier

The structural and molecular features of the BBB are key for normal brain function in that they control the bidirectional movement of ions, molecules, and cells between blood and brain.<sup>70,71</sup> The BBB results from the unique properties of cerebral endothelial cells that are adjoined by tight junction, have minimal vesicular transport across their cytoplasm (transcytosis), and are enriched with plasmalemmal influx and efflux transporters regulating the exchange of molecules between blood and brain and vice versa.<sup>70,71</sup> However, BBB integrity is also influenced by other cell types, including astrocytes and pericytes (intramural vascular cells present at the level of capillaries), as well as the extracellular matrix.<sup>70–72</sup>

Hypertension has profound effects on the BBB. Chronic hypertension is associated with BBB disruption in animal

models and in humans.<sup>73,74</sup> Loss of BBB integrity may be an early event in the pathogenesis of SVD.<sup>73,75,76</sup> In genetically hypertensive rats as in models of angiotensin II-dependent hypertension, reductions in CBF, loss of tight junction proteins, loss of BBB integrity, and white matter lesions have all been described.<sup>77,78</sup> Loss of BBB integrity has also been described in hypertensive patients<sup>79,80</sup> in association with SVD and white matter damage.<sup>74,75,79</sup> The mechanisms of the effect have not been fully elucidated, but one hypothesis is that hypoxia, caused by reduced CBF in susceptible white matter regions, leads to activation of hypoxia inducible factor-1 $\alpha$ -dependent genes, including metalloproteases, which may promote BBB damage.<sup>81</sup> Cellular elements beside endothelial cells are also involved in the BBB dysfunction. Pericytes, which are required for maintenance of the BBB,<sup>82</sup> may undergo degeneration during hypertension,<sup>83</sup> suggesting that loss or dysfunction of these cells may also contribute to disruption of BBB integrity. Extravasation of plasma proteins leading to vascular and perivascular inflammation and microvascular thrombosis are thought to be key pathogenic consequences of the BBB disruption contributing to white matter damage through inflammatory mediators and reactive oxygen and nitrogen species, but conclusive evidence is lacking, especially in humans.<sup>27</sup>

### Summary of Evidence

Hypertension induces adaptive changes in cerebral blood vessels that reduce stress on the vessel wall and protect downstream arterioles, capillaries, and venules from potentially damaging fluctuations in arterial pressure.<sup>23</sup> However, these structural alterations, in concert with the associated impairment of critical vascular regulatory mechanisms, may result in CBF reductions in regions of the subcortical white matter at risk for vascular insufficiency. Angiotensin II-dependent vascular oxidative stress is a critical factor in both the structural and functional cerebrovascular alterations induced by hypertension. In addition, alterations of endothelial cells and the BBB represent a key early event in SVD, but the pathogenic mechanisms remain poorly defined. An unexpected reciprocal interaction between hypertension and AD pathology has emerged whereby the hypertensive vasculopathy exacerbates the accumulation of A $\beta$  in brain and acts in concert with A $\beta$  to suppress vital cerebrovascular regulatory mechanisms. Although it remains to be established whether the deleterious effects of hypertension on cognition are reversible or lessened by treatment, experimental evidence suggests that some vascular changes induced by hypertension may be reversible with appropriate treatments.

### Cognitive Domains Targeted by Hypertension

This section describes the specific cognitive domains targeted by hypertension. Although the majority of early studies examining cognitive function in individuals with hypertension such as the MMSE (Mini-Mental Status Examination) have focused on global cognitive outcomes or composite measures of several cognitive tests, there is a growing literature on specific domains of cognitive function and possible differential association with hypertension. Studies focused on identifying specific domains may contribute to identifying the mechanism

by which hypertension impairs cognitive function, for example, microvascular effects versus brain atrophy, and informing the development, timing, and evaluation of pharmacological and behavioral interventions, for example, disease self-management and medication adherence. Cognitive function is assessed in studies of hypertension with a number of measures. The most common measures administered in these studies assess the specific domains of memory, executive function, and processing speed.

### Memory

Memory function includes tests of short-term memory, verbal learning, and working memory. Common short-term memory tasks include the Digits Forward Test, in which the subject is asked to repeat strings of numbers in same order in which they were read,<sup>84</sup> and immediate recall tasks, in which the subject is asked to recite back a list of words immediately after hearing them (eg, first trial of the Rey Auditory Learning Test).<sup>85,86</sup> Delayed memory is then assessed, usually after a 30-minute interval, with recall of short verbal stories or lists. Delayed memory can also be evaluated with 5-minute delayed recall, after a brief distraction task, of a list of words that have been used in sentences to promote encoding.<sup>84,87</sup> Working memory tasks also tap into executive function. The most common measure is the Digits Backwards Test, in which the subject is asked to repeat a string of words in the reverse order that they were read.<sup>84</sup>

### Executive Function

Executive function involves multiple brain processes and consequently is the cognitive domain that is most difficult to assess and has the most heterogeneity in measurements across studies. Of note, the widely used MMSE does not test domains related to executive function. Executive function is of particular importance for daily life because of the role it plays in decision making and problem solving, critical tasks for self-management of chronic illnesses. The most common tests used were the Controlled Oral Word Association Test (word fluency), category fluency (eg, animal naming), and the Trail Making Test Part B. The word fluency test requires subjects to generate as many words as possible beginning with the same letter of the alphabet (F, A, or S) in 60 seconds.<sup>88,89</sup> Category fluency, in which subjects are asked to name as many words as possible in a single category, for example, animals, is also used but is less difficult.<sup>90</sup> On average, older adults without cognitive impairment generate 12 to 16 words per minute and 19 to 22 animals per minute.<sup>89</sup> The Trail Making Test has 2 parts, A and B.<sup>91,92</sup> In part A, the subject is timed while drawing a continuous line to connect consecutive numbers (1–25). Part B times how long a subject takes to draw a continuous line connecting alternating letters (A–L) and numbers (1–13). The total time for Part B or the difference between the 2 parts (time for part B minus time for part A) is used as the outcome, with higher scores reflecting poorer performance. The difference score attempts to remove the speed element from the test evaluation and thus is more commonly used to examine executive function.<sup>89</sup>

### Speed of Processing

Although not a cognitive domain, reduced speed of processing leads to declines in other domains. Many tests of processing

speed also tap into attention and may be referenced as attention tasks. The 2 most common speed of processing/attention tasks are the Digit Symbol Substitution Test and the Trail Making Test Part A. The Digit Symbol Substitution Test is a paper and pencil task in which the subject is given 90 seconds to translate numbers into symbols using a key at the top of a page.<sup>84</sup> The total number of correct responses is used as the score. The Trail Making Test Part A, described above, uses the time required to draw a continuous line to connect numbers (1–25), with higher scores reflecting poorer (slower) performance.

### **Domains Affected by Hypertension Versus Clinically Diagnosed AD**

There is moderately strong evidence to support the claim that impaired and declining speed of processing and executive function are the most commonly encountered cognitive changes associated with hypertension.<sup>93–98</sup> The pattern of cognitive impairment associated with hypertension is often distinguished from the pattern associated with neurodegenerative dementias such as AD by the lack of consistent findings for an impact of hypertension on memory function, a defining characteristic of clinically diagnosed AD. However, the issue is complicated by the fact that hypertension, in addition to acting through cerebrovascular mechanisms, may be a risk factor for AD pathology (Effects of Hypertension on Cerebrovascular Structure and Function section and Hypertension and AD section).

### **Summary of Evidence and Methodological Considerations**

Although the evidence for an effect of late-life hypertension on specific cognitive domains is not conclusive, a few studies suggest that controlling BP from midlife to late life may provide a strategy to decrease the risk of late-life cognitive impairment, particularly in processing speed and executive function.<sup>94,96,99,100</sup> There is stronger and more consistent evidence for an association with systolic BP (SBP) than for diastolic BP (DBP), although this comparison has not been made uniformly across studies. This question warrants further examination.

Several methodological issues prevent direct comparison or meta-analysis of studies. Assessment of cognitive function is not standardized across studies, resulting in inconsistency in the domains assessed and even differences in the tests used to assess a single domain, with the most heterogeneity for the executive function. An effort by the National Institute of Neurologic Disorders and Stroke and the Canadian Stroke Network to harmonize assessment batteries for VCI offers standardized batteries of well-validated instruments for various interview lengths (eg, 60, 30, and 5 minutes).<sup>101</sup> In addition, there is considerable variability in the potentially confounding factors controlled across studies of hypertension and cognition. Most studies adjust for age, sex, and education. Fewer adjust for additional cardiovascular risk factors such as smoking, comorbid conditions (eg, diabetes mellitus), and body mass index.

### **Hypertension and Cognition: Observational Studies**

The goal of this section is to summarize the evidence from observational studies on the relationship between BP and

hypertension and cognitive health. The section is organized into 2 main subsections: evidence from cross-sectional studies and evidence from longitudinal studies. Each section is then further divided into the following categories based on the age at which BP was measured: midlife (age, 40–64 years), late life (age, 65–84 years), and oldest old (age  $\geq$ 85 years). We report findings on global cognition using measures such as the MMSE or the modified MMSE, and we report findings on specific cognitive domains such as executive function, memory, and processing speed (Cognitive Domains Targeted By Hypertension section).

### **Cross-Sectional Evidence on the Association Between BP and Cognition**

#### *Late-Life BP*

Evidence from cross-sectional studies has focused primarily on BP and cognition in late life. The evidence is mixed, with some studies suggesting that exposure to high BP is associated with worse cognitive function but other studies reporting the opposite association, a U-shaped association, or no association.

Several studies that examined the cross-sectional association between BP in late life and cognition suggested that having hypertension or exposure to high BP is associated with worse cognitive function.<sup>97,102–105</sup> Examples of such studies include the ARIC study (Atherosclerosis Risk in Communities) and NHANES (the National Health and Nutrition Examination Survey). Early findings from the ARIC study showed that subjects with a diagnosis of hypertension, defined as SBP  $\geq$ 160 mmHg or DBP  $\geq$ 90 mmHg, had lower scores on tests of processing speed and word fluency compared with those without hypertension.<sup>97</sup> More recent findings from NHANES similarly showed that having hypertension or high BP (SBP  $\geq$ 140 mmHg or DBP  $\geq$ 90 mmHg) at  $\geq$ 70 years of age was associated with worse performance on a test of global cognition.<sup>105</sup> However, other studies reported the opposite; that is, exposure to high BP in late life was associated with better cognitive performance.<sup>106,107</sup> For example, in the Honolulu-Asia Aging Study, having an SBP  $\geq$ 160 mmHg was associated with 51% lower odds of poor performance on a test of global cognition compared with having an SBP of  $<$ 100 mmHg.<sup>106</sup> A few other studies reported a U-shaped association.<sup>108</sup> For example, in less educated members of the Baltimore Longitudinal Study on Aging, both high and low DBPs were associated with poor performance on a neuropsychological test battery, including tests of executive function and confrontation naming (Boston Naming Test).<sup>108</sup> Furthermore, the Framingham Heart Study reported no cross-sectional association between BP in late life and cognitive function.<sup>109</sup>

#### *Oldest Old BP ( $\geq$ 85 Years of Age)*

Findings from a study in centenarians in Australia showed a cross-sectional association between BP and cognition such that higher SBP was correlated with better performance on a test of global cognition.<sup>110</sup> More recent findings from the 90+ Study in a retirement community in Southern California showed that the prevalence of hypertension did not differ between those who are cognitively normal and those with mild cognitive impairment (MCI).<sup>111</sup> However, the prevalence of hypertension was greatest in those with nonamnestic MCI compared with other

MCI, thus suggesting that hypertension-related cognitive impairment involves skills other than memory.

### Longitudinal Evidence on the Association Between BP and Cognition

Longitudinal studies offer a better study design than cross-sectional studies by ensuring a temporal association between a putative exposure and outcome. When repeated assessments of cognitive function are available, a rate of cognitive decline can also be calculated that may provide insight into the cause of cognitive impairment.

#### *BP in Adolescence*

A recent study in adolescents of the Seychelles Child Development study failed to find associations between BP measured at 12 to 15 years of age and cognitive function measured at both 17 and 19 years of age.<sup>112</sup> It may be that underlying physiological mechanisms linking hypertension and cognition may not be in play at such a young age. It is also possible that the tests used do not capture the variability in cognition that is associated with high BP at a young age.

#### *Midlife BP*

Recent findings in subjects of the CARDIA study (Coronary Artery Risk Development in Young Adults) with mean age of 25 years at baseline showed that higher burden of SBP over 25 years from young adulthood to middle age was associated with worse performance on several cognitive tests in midlife, including verbal memory, processing speed, and executive function, when the cohort was a mean of 50 years of age.<sup>93</sup> CARDIA is among the few studies that examined early to midlife BP and cognitive function in midlife. There is more substantial evidence addressing the longitudinal association between midlife BP and cognitive function in late life.<sup>98,103,106,113–115</sup> Overall, these studies consistently showed that having high SBP or a hypertension diagnosis in midlife was associated with worse cognitive performance in late life. Examples of such studies include the Framingham study,<sup>113</sup> which showed that higher SBP and DBP (increments of 10 mmHg) in stroke-free individuals in midlife were associated with worse performance on a composite global cognitive score and measures of attention and memory. Similarly, in the Honolulu-Asia Aging Study,<sup>106</sup> having a high SBP ( $\geq 160$  mmHg) in midlife was associated with a 2-fold increased risk of poor cognitive function on a test of global cognition 25 years later from a fully adjusted model. Findings from the Maine-Syracuse Longitudinal Study showed that higher baseline BP (increments of 10 mmHg) was associated with worse cognitive performance and a decline in visualization and fluid abilities up to 20 years later.<sup>115</sup> Even prehypertension, defined as SBP of 120 to 139 mmHg/DBP of 80 to 89 mmHg, in middle-aged women of the Women's Health and Aging Project was associated with reduced cognitive function on processing speed and verbal memory a decade later.<sup>116</sup>

However, few other studies reported either a U-shaped association or no association between midlife BP and cognition in late life. For example, the SABRE study (Southall and Brent Revisited) showed a U-shaped association between low and high DBP and cognitive impairment, measured as a composite cognitive score, 20 years later.<sup>117</sup> In addition, a

recent study in members of a French cohort of middle-aged adults showed that elevated BP (SBP/DBP  $\geq 130/85$  mmHg) or treatment in midlife was not associated with cognitive function, measured as a composite score and on subtests, nearly a decade later.<sup>118</sup>

Evidence on the association between midlife BP exposure and rate of cognitive change is scarce. Findings from the Framingham Offspring Cohort Study suggested that having midlife hypertension or an SBP  $\geq 140$  mmHg was associated with faster annual decline in executive function.<sup>99</sup> A recent study in subjects of the Maastricht Aging Study suggested that having midlife hypertension at baseline (ie, prevalent hypertension) was associated with cognitive decline at 6 and 12 years of follow-up on domains of verbal memory, executive function, and processing speed.<sup>96</sup> The cognitive decline observed in individuals developing hypertension after baseline (ie, incident hypertension) was more modest compared with the decline in those with prevalent hypertension, potentially suggesting that duration of exposure also may play a role. Another recent study in members of ARIC showed that midlife hypertension was associated with a significantly greater decline in global cognitive function over 20 years. Similar findings were observed with higher SBP in whites but not in blacks.<sup>94</sup>

#### *Late-Life BP*

Several studies have examined the association between late-life BP and cognitive function measured several years after BP was measured. Findings from these studies are inconsistent. Several large-scale studies such as the Chicago Health and Aging Project,<sup>119</sup> the Longitudinal Study on Aging,<sup>120</sup> the Sacramento Area Latino Study on Aging,<sup>121</sup> and WHIMS (Women's Health Initiative Memory Study)<sup>122</sup> failed to find an association. However, other studies reported a U-shaped association<sup>107,123</sup> or a linear association.<sup>95,124,125</sup> For example, results from the Duke Population Studies of the Elderly found a U-shaped association between SBP and cognitive decline over 3 years, although this association was observed only in white subjects.<sup>123</sup> Results from ELSA (English Longitudinal Study on Aging) showed linear associations such that higher SBP and DBP were associated with lower scores on a global cognitive index and a memory index  $\approx 8$  years later. Further findings showed that having an SBP  $\geq 160$  mmHg was associated with worse performance on the global and memory cognitive indexes 8 years later compared with having an SBP  $< 140$  mmHg.<sup>124</sup> The ARIC study<sup>95</sup> showed that having hypertension at baseline, defined as SBP/DBP  $\geq 140/90$  mmHg or taking antihypertensive medications, was associated with a decline in processing speed over a 6-year period. Findings in community-dwelling members without dementia of the Women's Health and Aging Study II showed that having an SBP  $\geq 160$  mmHg was associated with a greater incidence of cognitive impairment over a 9-year period as measured on executive function.<sup>125</sup>

#### *Oldest Old BP*

There are only a handful of longitudinal studies of BP and cognition in the oldest old. Findings from the Leiden 85-Plus study were inconsistent; although some findings did not show an association between BP and change in global cognitive function over 3 years,<sup>126</sup> other analyses of the same study

showed that a 10-mmHg increase in SBP was associated with better cognitive performance on a global test and several domain-specific tests.<sup>127</sup> These results were further confirmed in a more recent analysis.<sup>128</sup> Furthermore, recent findings in subjects of the Newcastle 85+ study showed that having high BP, defined as SBP/DBP  $\geq$ 130/85 mmHg or treatment, was associated with better global cognitive function over 5 years.<sup>129</sup>

### Summary of Evidence

There is consistent evidence that BP in midlife is associated with altered cognitive function in both midlife and late life. The association of BP in late life and oldest old age with cognition is less clear, with evidence of both harmful and beneficial effects of high BP on cognition. Associations were observed mostly with tests of global cognition and executive function, which is not surprising given that vascular risk factors influence executive functioning to a greater extent and are not necessarily related to memory (Cognitive Domains Targeted by Hypertension section). The inconsistency of results across studies, especially in older age, may reflect differences in the cognitive domains assessed, differences in aspects of study design, including length of follow-up and how the rate of cognitive change was modeled, differences in characteristics of the study populations and varying age ranges, and adjustment for shared determinants that may confound the hypertension-cognition association. Reverse causation may also contribute to the observed association between BP and cognition, especially in studies with cross-sectional design. Cognitive impairment is a process that unfolds over decades, thus presenting a challenge to establishing temporality. More research is needed to elucidate the causal link between BP and cognition and to better understand the role of medication in the observed associations. The relationship between BP and cognitive function remains relatively underexplored in minority and racially or ethnically diverse populations. Finally, there remain inadequate examination and reporting of potential sex differences in the effects of BP and hypertension on cognition. Future studies need to closely examine and report sex-specific associations.

### Interaction With Other Risk Factors, Including Genetics

This section explores the possible impact of cardiovascular and other risk factors on the cognitive deficit associated with hypertension, focusing on age, sex, race/ethnicity, obesity and central obesity, metabolic syndrome/insulin resistance/diabetes mellitus, inflammatory biomarkers, lipids, smoking, occupation, education, diet, and air pollution. Possible interactions with atrial fibrillation, arterial stiffness, cardiac function, carotid intima-media thickness/stenosis, and stroke were not examined because these intermediate subclinical and clinical disease states could lie along the causal pathway between hypertension and cognitive impairment. However, genetic factors that might underlie both hypertension and cognition were also examined, focusing on genes such as *APOE* that are known to affect cognition independently, genes thought to be associated with vascular dementia and a vascular pattern of cognitive impairment, and genes affecting the risk of stroke, hypertension, and cognitive impairment.

### Interaction With Age, Sex, and Metabolic Traits

#### Age

An interaction with age has been shown in multiple studies, with higher BP and hypertensive status being associated with worse cognition in younger<sup>130</sup> and middle-aged adults (Hypertension Treatment Over the Life Course section). On the other hand, either a J-shaped association of SBP with cognition<sup>108</sup> or an association of higher DBP with better cognition and slower rates of decline in cognition was noted in older adults. Thus, a study of centenarians showed a positive association between SBP and cognitive performance.<sup>110</sup> This age interaction has been shown both for cognitive function in individuals free of dementia and when the end point of clinical dementia or AD was considered (Hypertension and AD section). Conversely, analysis of 1695 Framingham Study subjects failed to show an interaction with age over the 55- to 88-year range when individuals with concomitant stroke were excluded, and a study of 1130 subjects in the ARIC study also showed no age interaction.<sup>100,131</sup>

#### Sex

The interaction of male or female sex with hypertension in affecting cognition has not been investigated in detail, although a single study of 1034 women suggested an interaction of hypertension with menopausal status. Among postmenopausal women, cognitive performance on the Mini-Boston Naming Test was worse in hypertensive women compared with normotensive women, whereas among premenopausal women, no difference was observed between hypertensive and normotensive women.<sup>132</sup>

#### Metabolic Traits

An interaction of various metabolic and vascular risk factors such as diabetes mellitus with hypertension has been documented to increase the risk of stroke<sup>133</sup> and thus to indirectly increase the risk of dementia. However, studies that have looked for an interaction of diabetes mellitus with hypertension and an adverse impact on cognition have typically found independent, additive effects rather than a synergistic interaction of these 2 risk factors.<sup>134</sup> Among the various metabolic dysfunctions noted in diabetes mellitus, insulin resistance appears most likely to interact with hypertension. A measure of central obesity (having a waist-to-hip ratio in the top quartile) was noted to have a synergistic interaction with severity (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure stage) of hypertension on the impact on visual memory performance in the Framingham Offspring study,<sup>135</sup> and a small study has reported an adverse impact of concurrent elevations in BMI, waist-to-hip ratio, and insulin resistance (homeostatic model assessment–insulin resistance) on cognition in hypertensive patients.<sup>53</sup> Either no evidence or limited evidence was found for interactions of BP or hypertension with smoking, occupation, education, diet, and air pollution on their impact on cognition, although several of these risk factors are known to have synergistic interactions with hypertension in increasing the risk of cardiovascular events, including clinical stroke.



### Interaction With Circulating Biomarkers

In a small study from Maastricht, in hypertensive individuals, higher circulating levels of markers of endothelial activation (eg, vascular cellular adhesion molecules and selections) and of inflammation (eg, C-reactive protein) were found to be associated with worse cognition, and in a Japanese study that has not been replicated, pentraxin-3, another marker of inflammation, was associated with worse cognition in hypertensive individuals. However, these studies included only hypertensive individuals and could not specifically assess possible interactions between BP and inflammation.<sup>136</sup> There are only a few reports of interactions between adverse lipid profiles (elevated low-density lipoprotein, lower high-density lipoprotein, and higher triglycerides) and BP in their impact on cognition<sup>137</sup>; these seem to be in the setting of a metabolic syndrome with concomitant insulin resistance or explained by an *APOE*  $\epsilon$ 4 genotype.

### Interaction With Genetic Markers

An interaction between the *APOE*  $\epsilon$ 4 allele and many cardiovascular risk factors in their impact on cognition has been shown in various studies, and this appears to be true for hypertension in most<sup>138,139</sup> but not all of these studies.<sup>140</sup> The Honolulu-Asia Aging Study followed up 3065 Japanese American men over 26 years and observed an interaction of the *APOE*  $\epsilon$ 4 genotype and an SBP  $\geq$ 160 mmHg in their impact on cognition with relative risks of 2.6 and 13, respectively, of impaired cognition when individuals who had hypertension but no *APOE*  $\epsilon$ 4 allele and those with both risk factors were compared with a control group with neither.<sup>141</sup> An Australian study of 1467 community subjects who were 60 to 64 years of age at baseline and examined for cognitive performance 3 times over 8 years noted that the *APOE*-hypertension interaction, but not a *APOE*-mean arterial pressure interaction, was associated with a small but statistically significant increase in the rate of decline of episodic memory, verbal ability, and global cognition.<sup>142</sup> A similar interaction was demonstrated in 563 subjects of the Seattle Longitudinal Study in whom cognitive change was assessed over a 21-year period.<sup>143</sup> Recently, several genetic variants have been identified to determine cognitive performance in the domains of verbal memory, fluid intelligence (the general intelligence factor), and executive function in older adults. In these older adults, a variant in the *KIBRA* gene showed an association with worse verbal memory, an effect that was restricted to individuals with hypertension and was larger in hypertensive women compared with men.<sup>144</sup>

### Summary of Evidence

There are limited data on possible interactions between demographic, genetic, and vascular risk factors and hypertension in their impact on age-related cognitive decline and risk of AD. Age is an important factor, with high BPs in midlife and lower BPs in late life increasing the risk of poor cognition. Menopausal status, insulin resistance, inflammation, and the *APOE*  $\epsilon$ 4 genotype may each potentiate cognitive decline in hypertensive individuals. The mechanisms underlying these putative interactions remain uncertain, although in the case of *APOE*, the tau pathway has been implicated in a few studies.

### Hypertension and AD

Hypertension is an important vascular risk factor and may influence the risk of MCI or dementia resulting from AD, the neuropathological findings in AD, and the corresponding neuroimaging and cerebrospinal fluid (CSF) biomarkers. The purpose of this section is to explore the relationship between hypertension and the risk for AD and its neuropathological manifestations, as well as neuroimaging and CSF biomarkers.

### Hypertension and AD Risk: Epidemiological Studies

Examination of the associations between elevated BP and the risk of clinically diagnosed AD is complicated by several factors, and the associations remain poorly understood. Observational studies suggest that higher BPs before the age of 65 to 70 years increase the risk of AD. In older adults, lower SBP appears to be associated with an increased risk of developing AD, whereas higher DBP may lower risk. Genetic variants associated with higher BP may reduce the risk of developing AD pathology.<sup>145</sup> Here, we summarize the epidemiological evidence and then discuss the challenges in interpretation.

#### *Epidemiological Evidence*

Cross-sectional analyses in the Hisayama Study,<sup>146</sup> in the Canadian Health and Aging Study,<sup>147</sup> and in a convenience sample of 1259 Medicare enrollees<sup>148</sup> showed an association of high BP with greater overall risk of dementia and with risk of vascular dementia but not with risk of clinically diagnosed AD. The Women's Health Initiative showed an association of higher BP with greater risks of incident MCI and dementia that disappeared after adjustment for possible confounders.<sup>122</sup> The Kungsholmen study found no association of BP with dementia risk over 6 years of follow-up except at the extremes of SBP ( $>$ 180 mmHg) and DBP ( $<$ 65 mmHg).<sup>149</sup> In contrast, other studies in older adults suggest a protective effect of mild hypertension on AD dementia risk.<sup>150–154</sup> A U-shaped association with the lowest risk for AD dementia in individuals with a DBP in the 70– to 90-mmHg range was noted in the Chicago Health and Aging Project.<sup>119</sup> Unlike the findings in older adults, recent studies have observed an association of higher midlife BPs or midlife categorical hypertension with increased late-life dementia risk, including studies in Finnish,<sup>155,156</sup> Japanese Northern Californian,<sup>157</sup> and Hawaiian cohorts.<sup>158</sup> However, these studies did not separately examine the risks of developing AD versus vascular dementia.

#### *Challenges*

Hypertension, however defined, is associated with an increased risk of stroke in a graded, continuous manner, and stroke, in turn, increases the risk of dementia.<sup>12,159</sup> Many epidemiological studies are confident in their clinical diagnosis of dementia but acknowledge uncertainty resulting from limited resources in assigning a subtype of dementia. Thus, if individuals with hypertension were more likely to manifest clinical symptoms of dementia at the same stage of AD pathology, this could lead to a spurious association of hypertension with AD dementia. Conversely, individuals with hypertension are also more likely to be categorized as having

vascular or mixed dementia rather than “pure” AD, and this diagnostic bias could result in an apparent protective effect of hypertension on clinically diagnosed AD.

Another reason for the complexity of the association between BP and AD is the many ways in which BP can be assessed (SBP, DBP, pulse pressure,<sup>160</sup> mean arterial pressure, and arterial stiffness measured as carotid-femoral pulse wave velocity on tonometry) and the differential impact of each dimension on brain health and AD pathology. SBP in individuals at higher risk of subsequent dementia may rise faster starting in midlife and decline faster at older ages compared with SBP in other individuals.<sup>161</sup>

There appears to be a progressive decline in BP in the early stages of dementia that may be attributable directly to the neurodegenerative process affecting brainstem and hypothalamic nuclei regulating arterial pressure and systemic metabolism,<sup>162,163</sup> may result from the associated systemic changes such as weight loss and increased frailty, or may be secondary to the onset of cardiovascular diseases such as myocardial infarction and congestive heart failure that can reduce the ability of the heart to maintain systemic and cerebral perfusion pressures. Thus, BPs measured 1 to 10 years before the onset of clinical AD may be biased by reverse causality and may not represent the pressures experienced before the onset of the AD pathological process.

In summarizing the literature, 2 recent weighted meta-analyses of cohort studies, including 6 studies of individuals with MCI<sup>164</sup> and 28 studies of cognitively normal individuals, that specifically considered the end point of clinically diagnosed AD<sup>165</sup> failed to find an association of any BP measure with risk of developing AD, whereas an earlier meta-analysis of 18 cohort and case-control studies had suggested an association of elevated midlife DBP with increased risk of AD and an inverse association of late-life hypertension with lower risk of AD; both effects were small.<sup>166</sup> Secular trends in the treatment of hypertension in midlife might be having an impact. The risk for dementia in Japanese American subjects treated with antihypertensives for >12 years starting in midlife was lower compared with the risk in hypertensive individuals not on treatment (for dementia: hazard ratio, 0.40; 95% confidence interval, 0.22–0.75; and for AD: hazard ratio, 0.35; 95% confidence interval, 0.16–0.78) and was similar to the risk in normotensive individuals.<sup>167</sup> An added consideration is that antihypertensives may have class-specific effects on AD pathology that are independent of their BP-lowering effect<sup>168,169</sup> (Effects of Hypertension on Cerebrovascular Structure and Function section). In this regard, it is of interest that individuals with genetic variants associated with higher BP and use of antihypertensive agents have a reduced risk of AD.<sup>145</sup>

### **Hypertension and AD Neuropathology**

In all of its target organs, hypertension causes dysfunction through alterations in vascular function (Effects of Hypertension on Cerebrovascular Structure and Function section). However, there are some reports that hypertension might have an impact on AD pathology. In Japanese American men (n=243) in the Honolulu-Asia Aging Study, there was an association between midlife BP and burden of NFTs at death, roughly 3 to 4 decades later.<sup>170</sup> Elevated SBP at midlife was

associated with low brain weight and neocortical and hippocampal neuritic plaques, whereas elevated DBP at midlife was associated with increased NFTs in the hippocampus. Another clinical-pathological study from the Bronx, NY,<sup>171</sup> that included both men and women (n=291) found that medication-treated hypertensive individuals had significantly lower levels of neuritic plaques and NFTs compared with nonhypertensive individuals. Untreated hypertensive individuals had more NFTs and neuritic plaques than the treated hypertensive individuals but were not different from the normotensive individuals. The authors emphasized the role of antihypertensive medications over hypertension itself because of the pattern of results in treated versus untreated hypertensive individuals and suggested a protective effect of medications. A clinical-pathological study involving 84 individuals with neuropathological diagnoses of AD with or without cerebrovascular changes from San Diego<sup>172</sup> found that antemortem vascular risk factors that included hypertension but also diabetes mellitus, heart failure, atrial fibrillation, peripheral vascular disease, and smoking were associated with lower Braak stage. The study was underpowered to examine hypertension by itself. Because it is difficult to quantify cerebrovascular changes, these results could have been attributable to greater vascular burden. Along those lines, an earlier study from this group found that pulse pressure was associated with cerebrovascular lesions (large-vessel atherosclerosis, infarcts of any size) at autopsy,<sup>173</sup> along with no associations with Braak stage or amyloid angiopathy. A study from Seattle Group Health reported an association between systolic hypertension and the presence of >2 microinfarcts in younger subjects (age, 65–80 years), but there were no associations with AD-type lesions (Braak stage or Consortium to Establish a Registry for Alzheimer’s Disease plaque score) or Lewy bodies.<sup>174</sup> There were no associations with vascular lesions in older individuals (>80 years old at entry).

In summary, the evidence linking antemortem hypertension to postmortem neuropathological changes seen in AD is modest and confounded by differential survival, indication bias, and small numbers. Although results from the Honolulu-Asia Aging Study<sup>170</sup> support the idea of an overlap between hypertension and AD pathophysiology, other reports do not. With antemortem amyloid and tau positron emission tomography (PET) imaging now available, prospects for determining the true relationship between hypertension and AD pathological changes are much brighter.

### **Impact of Hypertension on Biomarkers and Association With AD**

Hypertension and AD-type pathophysiology appear to share a common pathogenesis in several imaging features: white matter hyperintensities (WMHs), cerebral microbleeds, and brain volume/atrophy.

#### **White Matter Hyperintensities**

WMHs, as detected by fluid-attenuated inversion recovery magnetic resonance imaging (MRI), are widely regarded as lesions associated with cerebrovascular disease<sup>175–177</sup> (see elsewhere for a discussion of relevant white matter imaging modalities<sup>75,178,179</sup>). Hypertension is the most important risk factor for the development of WMH.<sup>99,180–182</sup> Hypertension in

general,<sup>180,183–185</sup> high SBP,<sup>99,185–190</sup> high DBP,<sup>186,189,191–193</sup> low DBP,<sup>194</sup> pulse pressure,<sup>185</sup> mean arterial pressure,<sup>195,196</sup> pulse wave velocity,<sup>197</sup> and arterial stiffness<sup>198</sup> have all been associated with WMHs, and it is not clear that one measure of BP predominates over the others in magnitude of the association. Treatment adds considerable complexity to the relationship between hypertension and WMH, but a few clinical trials have shown that WMH progression is reduced with antihypertensive treatment.<sup>199,200</sup> Diffusion tensor imaging is another imaging technique for examining anatomic integrity in white matter. Changes in fractional anisotropy or mean diffusivity have been associated with some aspect of hypertension,<sup>201–206</sup> although not invariably.<sup>207</sup> Carriage of the *APOE*  $\epsilon 4$  genotype has been associated with higher levels and faster rates of accumulation of WMH in some studies<sup>208,209</sup> but not others.<sup>210</sup> Some studies have claimed that the combination of hypertension and carriage of the *APOE*  $\epsilon 4$  genotype was linked to more WMHs.<sup>211,212</sup> We found no studies claiming interactions at the mechanistic level between hypertensive pathophysiological process and AD pathophysiological processes on WMH burden. On the other hand, there is evidence that cerebrovascular disease and AD pathophysiology have at least additive effects at the clinical level.<sup>213–216</sup> Thus, although cerebrovascular mechanisms do not worsen AD processes, the combination of the two may lead to earlier and greater cognitive decline.

#### **Cortical Microbleeds**

Cortical microbleeds, microhemorrhages of 1 to 3 mm in diameter that often are attributable to cerebral amyloid angiopathy,<sup>217</sup> are also associated with hypertension.<sup>182,218–221</sup> Deep locations, that is, the putamen and thalamus, are much more likely to be associated with hypertension, whereas cortical locations are more likely to be associated with carriage of the *APOE*  $\epsilon 4$  allele<sup>209,222,223</sup> or with elevated A $\beta$  levels by PET imaging.<sup>224</sup> In patients with AD, hypertension increased the likelihood of cortical microbleeds,<sup>225</sup> but that effect could be additive or interactive. We otherwise uncovered no evidence for or against an interaction between hypertension and A $\beta$  burden for cortical microbleeds. Cortical microbleeds are modestly related to cognition<sup>197,226</sup> but not to decline in individuals with AD.<sup>227</sup>

#### **Brain Atrophy**

In some reports, loss of brain volume has been associated with hypertension,<sup>190,194,228,229</sup> mean arterial pressure,<sup>196</sup> or arterial stiffness,<sup>198</sup> but other studies failed to demonstrate the association<sup>99,195,230,231</sup> (Beauchet et al<sup>232</sup> provide further discussion). Treatment effects might confound the interpretation of associations.<sup>233</sup> The mechanisms whereby hypertension causes brain volume loss are not clear. To the extent that WMHs are also associated with brain volume,<sup>208,234–240</sup> the effects of hypertension on brain volume could be mediated via loss of white matter integrity. Other potential mechanisms could include microinfarction, remote effects of axonal injury in white matter, and an interaction with AD processes such as trafficking of damaged proteins in the perivascular spaces.<sup>241</sup> Hypotension and falling BP over time are also associated with loss of brain volume.<sup>242</sup> Indeed, the U-shaped relationship between BP and brain integrity is an important feature of the relationship

between BP and late-life cognitive impairment (Hypertension and Cognition: Observational Studies section).

#### **A $\beta$ PET Imaging**

Only a few studies have examined associations between hypertension and A $\beta$  levels by PET imaging. In a subset of subjects from a ginkgo clinical trial who underwent Pittsburgh compound B PET imaging, there was an association between pulse wave velocity and higher brain amyloid levels<sup>243</sup> that was independent of BP and *APOE*  $\epsilon 4$  genotype. In a group of middle-aged volunteers, an association of SBP and pulse pressure with burden of A $\beta$  by PET imaging was seen,<sup>244</sup> but in older individuals, concurrent DBP but not SBP was associated with A $\beta$  burden by Pittsburgh compound B PET.<sup>245</sup> Another study found an interaction between the *APOE*  $\epsilon 4$  genotype and hypertension and Pittsburgh compound B PET.<sup>246</sup> This same group also found a main effect for pulse pressure.

#### **CSF Biomarkers for AD**

We found only a few studies that examined associations of BP and CSF markers of AD. In a group of cognitively normal individuals who had CSF examinations, there was an association of pulse pressure with increased phospho-tau and reduced A $\beta 42$ ,<sup>247</sup> a finding that was replicated in an independent cohort.<sup>248</sup> Another study of CSF biomarkers showed an interaction between the *APOE*  $\epsilon 4$  allele (especially  $\epsilon 4$  homozygosity) and hypertension in elevating CSF tau and phospho-tau levels.<sup>249</sup> However, in that study, there was no similar interaction of hypertension and carriage of an  $\epsilon 4$  allele on CSF A $\beta$  levels. The relevance of these findings to the progression of AD requires further study.

#### **Summary of Evidence**

Several epidemiological and clinical pathological studies have reported a link between hypertension and AD. However, a challenge to the interpretation of the relationship between hypertension and AD is the substantial lag from the onset of the study of hypertension to the time of pathological diagnosis of AD. The growing availability of amyloid PET imaging and structural MRI offers the opportunity to better understand the role of hypertension and brain pathology in vivo. In population-based or special (enriched) cohort studies, large sample sizes would be needed to distinguish separate roles for SBP, DBP, pulse pressure, mean arterial pressure, and carotid-femoral pulse wave velocity on each of the imaging features. Longitudinal studies would be needed to assign priority to assessing hypoperfusion, white matter changes, cortical volumetric changes, microbleeds, and amyloid accumulation to understand their interrelationships. Future imaging techniques that can detect specific target involvement will be needed to understand what cells or cellular elements are the site of the initial pathogenic insult of hypertension. The cell types and end points that are most amenable to therapy are still unclear.

### **Hypertension and Cognition: Clinical Trials of BP Lowering**

This section examines available data from clinical trials on the effect of hypertension treatment on cognitive function. We excluded studies that were not randomized, prospective trials with a primary or secondary outcome relating to cognitive

status. Using the search criteria outlined in Methods, we identified 27 trials for consideration. We considered criteria based on sample size and excluded studies with <500 individuals per treatment arm. This is an arbitrary cut point based on a generic power analysis using data reported by Hypertension in the HYVET-COG (Very Elderly Trial Cognitive Function Assessment) for dementia events (36 of 1000 in the control group and 24 of 1000 in the treatment group<sup>250</sup>) and differences in end-trial MMSE measured in SYST-EUR (Systolic Hypertension in Europe).<sup>251</sup> All studies were further assessed for bias according to the Cochrane Collaborations checklist.<sup>252</sup>

### Trial Descriptions

Nine trials met the general inclusion criteria. Most trials testing cognition were based on the total main trial population (SPS3 [Secondary Prevention of Small Subcortical Strokes Trial], PROGRESS [Perindopril Protection Against Recurrent Stroke Study], SCOPE [Study on Cognition and Prognosis in the Elderly], PROFESS [Prevention Regimen for Effectively Avoiding Second Strokes], ONTARGET [Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial], TRANSCEND [Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease], and SHEP [Systolic Hypertension in the Elderly Program]), were ancillary studies embedded in a subsample of the main trial,<sup>253</sup> or included selected sites (SYST-EUR<sup>251</sup>). Sample sizes ranged from 1439 to 25620, and mean patient age ranged from 62 to 83 years. Follow-up time ranged from  $\approx$ 2 years (SYST-EUR)<sup>251</sup> to  $\approx$ 5 years (ONTARGET/TRANSCEND<sup>254</sup>). Two trials were stopped early because they reached their primary end point (SYST-EUR<sup>251</sup> and HYVET<sup>250</sup>). The SPS3 antiplatelet arms were stopped early because of futility and evidence of harm.<sup>255</sup>

Target populations for the trials differed. The main inclusion of some trials was based on BP levels<sup>256</sup> (SHEP<sup>257</sup> and HYVET<sup>250,251</sup>) or resistance to a particular class of antihypertensives (TRANSCEND).<sup>254</sup> Other trials included patients with cardiovascular disease or at high risk for cardiovascular events: The ACCORD MIND trial (Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes) included individuals with long-standing diabetes mellitus at high risk for cardiovascular events<sup>253</sup>; ONTARGET included patients with subclinical evidence of cardiovascular risk<sup>254</sup>; and some trials included patients with a recent to more remote history of different stroke subtypes, that is, ischemic and lacunar (PROFESS, SPS3, and PROGRESS).<sup>258–261</sup>

The mean BP levels at baseline have declined over time, consistent with evolving evidence supporting lower BP treatment goals. Thus, the earlier trials (SHEP,<sup>262</sup> SYST-EUR,<sup>251</sup> and SCOPE<sup>256</sup>) included people now classified in the stage 2 hypertension range. More recent trials included patients with qualifying BP levels that fell into the stage 1 hypertension range, so mean baseline BPs were lower.

Treatment protocols have also changed, and designs have become more complex. The range of designs include testing a single drug against placebo (TRANSCEND<sup>254</sup>; a single drug versus placebo, allowing open-label antihypertensive treatment in the placebo arm if needed in SCOPE<sup>256</sup>) or a primary drug followed by a standardized step procedure

with a protocol-driven sequence for adding additional drugs (HYVET,<sup>250</sup> SYST-EUR,<sup>251</sup> SHEP,<sup>257</sup> and SCOPE<sup>256</sup>) or without specified BP goals (SPS3,<sup>259</sup> PROFESS,<sup>258</sup> PROGRESS,<sup>260</sup> and ONTARGET/TRANSCEND<sup>254</sup>) ACCORD MIND<sup>253</sup> tested 2 therapeutic strategies with different SBP goals, <120 versus <140 mm Hg. Several trials used a 2-by-2 factorial design that allowed a test of >1 intervention. The 2-by-2 factorial of SPS3 had 2 arms comparing different SBP goal–defined therapeutic strategies and comparing a dual antiplatelet therapy with aspirin plus placebo.<sup>259</sup> The PROFESS trial had 4 arms that tested antiplatelets, angiotensin II receptor inhibitors, and placebo<sup>258</sup>; ONTARGET had 3 arms comparing an angiotensin-converting enzyme inhibitor, angiotensin II receptor inhibitors, and a combination of drugs.<sup>254</sup> The achieved reduction in BP (SBP/DBP) ranged from  $-0.9/0.6$  in the telmisartan versus ramipril arm in the ONTARGET trial<sup>254</sup> to  $15/5.9$  in HYVET.<sup>250</sup>

### Cognitive Outcomes

The most widely used test, as a single and primary outcome, has been the MMSE, which is a 30-point test of global cognition. The SPS3 trial<sup>259</sup> used the Cognitive Abilities Screening Instrument, another, longer test of global cognitive function. ACCORD MIND<sup>253</sup> had as its primary outcome psychomotor speed (Digit Symbol Substitution Test; Cognitive Domains Targeted by Hypertension section). The MMSE score was used in several metrics to define outcome, including the absolute MMSE score, percent scoring <24 (HYVET,<sup>250</sup> ONTARGET,<sup>254</sup> SCOPE,<sup>256</sup> and PROGRESS<sup>260</sup>), or a drop of 3 points (PROGRESS<sup>260</sup>). The MMSE was also used as a screening instrument to identify people for additional workup for dementia (HYVET<sup>250</sup> and PROGRESS<sup>260</sup>) or to define dementia (ONTARGET<sup>254</sup>). The second most frequent outcome was dementia, which was diagnosed by investigator-assessed and specialist-confirmed diagnosis of dementia (ONTARGET<sup>254</sup> and PROFESS clinical impression<sup>258</sup>), a local investigator following international criteria (SCOPE<sup>256</sup>), and an examination of screen-positive individuals by a local specialist following international guidelines and then central adjudication (PROGRESS<sup>260</sup>; SCOPE,<sup>256</sup> SYST-EUR,<sup>250,251</sup> and SHEP<sup>257</sup>). Trials that aimed to subtype the dementia used the Hachinski ischemic score<sup>263</sup> in addition to the MMSE and clinical assessment to assess the likelihood of a cardiovascular contribution and a computed tomography scan to image cerebrovascular lesions.

### Other Measures of Brain Function and Structure

Three trials had imaging substudies (MIND,<sup>253</sup> PROFESS,<sup>264</sup> and PROGRESS<sup>199</sup>) to test whether the intervention was related to the development or progression of pathology in the brain, as measured by MRI. PROFESS imaged 777 people on average 27 months apart; in that subsample, there were no differences between treatment groups<sup>264</sup> in BP levels or in the outcome, progression of WMHs assessed by fluid-attenuated inversion recovery MRI. In the PROGRESS substudy of 192 subjects followed up for 36 months, a significant slowing of WMH progression was detected between treatment groups.<sup>199</sup> The 314 MRIs acquired at baseline and 40 months later in ACCORD MIND showed that total brain volume had declined more in the group with intensive versus standard

strategy to lower BP.<sup>253</sup> Few trials assessed >1 cognitive function in all (SPS3)<sup>253,259</sup> or a subsample of subjects (SHEP<sup>262</sup> and SCOPE<sup>265</sup>). A SCOPE substudy (n=257)<sup>265</sup> found suggestive evidence of a small effect of treatment on attention and episodic memory tests but not working memory or executive function. Other trials found no treatment differences in test scores.<sup>253,259,262</sup>

### Results of Clinical Trials

Only 1 trial, SYST-EUR, had a marginally significant result suggesting the treatment benefit of reducing dementia (21 versus 11 patients;  $P=0.05$ ), an effect that persisted during an open follow-up phase.<sup>251,266</sup> The PROGRESS trial, using a definition of “dementia (or cognitive decline) after stroke” and “other dementia (cognitive decline),” found a significantly ( $P=0.03$ ) reduced risk in the patients with treated dementia after stroke compared with control subjects (43 versus 65) and an overall reduction in cognitive decline in the treated group, with the difference attributable mainly to the cognitive decline with stroke group.<sup>260</sup> Other trials report no differences on cognitive test performance between intervention and control arms. Post hoc analyses in several trials indicate that within treatment arms, there was a negative association of more cognitive decline in those with a smaller decrease in BP (SYST-EUR and ONTARGET).<sup>251,259</sup>

### Evidence for a Particular Class of Antihypertensive Drug

A meta-analysis in 2011 of 8 trials reviewed here found that overall there was no effect of BP lowering on the risk for dementia.<sup>267</sup> However, there was a suggestion that calcium channel blockers may slightly reduce the incidence of dementia, but the authors note that the benefit could be attributable mostly to the amount of BP lowering achieved in those trials. Such comparisons point out the difficulty in identifying any one drug class as being particularly beneficial for cognition: There is a confounding between baseline BP, number of drug classes used to lower BP, and the amount of BP lowering achieved in the trials. The evidence suggests that there is no Class A evidence for treating hypertensive patients (>160/90 mmHg) with no apparent cardiovascular disease to preserve cognition. At lower levels of BP and in trials based on patients with preexisting cardiovascular disease, the existing trials have been uniformly negative. However, this conclusion should be tempered given several sources of bias in these trials and the strength of the trials to test the hypotheses. These are examined next.

### Possible Sources of Bias and Heterogeneity of Results

Five studies reported the power of their analyses to detect treatment differences related to the cognitive outcomes.<sup>250,251,253,258,260</sup> There is a possibility that the trials using the MMSE as their primary outcome were underpowered for the small differences that have been reported. In multicenter, multicultural studies, standardized assessment of dementia is important, particularly for mild cases of dementia, for which the cutoff for clinical dementia can vary substantially. Several trials reporting dementia outcomes do not provide sufficient information to determine whether and how assessments of

dementia followed standardized protocols to fulfill international guidelines (ONTARGET,<sup>254</sup> PROFESS,<sup>258</sup> SCOPE,<sup>256</sup> PROGRESS<sup>260</sup>, HYVET,<sup>250</sup> SYST-EUR,<sup>251</sup> and SHEP<sup>262</sup>). There is also a lack of documentation about the blinding of the individuals administering tests or rendering a dementia diagnosis.

Separation of BP levels between treatment arms was, in some of the trials testing specific drugs, attenuated because the control group was treated with antihypertensive drugs. This was a particular issue in the early trials when ethics guidelines called for treating very high BP (SCOPE,<sup>256</sup> SHEP,<sup>262</sup> and SYST-EUR<sup>266</sup>), although the definition of very high varied.

Finally, negative trial results could be attributable, in some trials, to the loss of data from those who either did not receive the full BP intervention or missed cognitive assessments.

### Possibility of Finding Effects and Sources of Heterogeneity

Even in the absence of specific bias in implementation or reporting, it is important to consider the overall question of whether the trials were appropriately designed to test the efficacy of BP lowering to reduce cognitive decline/dementia. One factor to consider is whether the outcome measured was appropriate for the subjects' age. The MMSE or a similar test of global cognition was used as the only cognitive measure<sup>250,254,256,258,259</sup> in subjects from 60 to 65 years of age. Others were investigating dementia in patients of that age. This age range is likely too young to see a detectable change on the MMSE because that test has a low ceiling and a non-linear pattern of change and is unlikely to provide cases of incident dementia, which begins to increase in incidence after 80 years of age. Furthermore, the MMSE was designed to screen for cognitive deficits caused by AD and may miss some of the major cognitive changes thought to accompany vascular-related cognitive impairment.<sup>3</sup>

Another issue about the strength of the completed trials investigating BP lowering and cognition is the likelihood of detecting clinically relevant outcomes during the short intervention periods. Several trials included a relatively cognitively healthy group with a mean MMSE score of 29 of 30 points. Post hoc analyses of several studies suggested that those who were more cognitively compromised, but still without dementia, may benefit more from short-term interventions (SCOPE<sup>268</sup> and ONTARGET/TRANSCEND<sup>254</sup>).

Finally, if loss to follow-up or stopping treatment is related to cognitive impairment, then differences between treatment arms may be attenuated, with negative results. A simulation analysis based on SHEP<sup>269</sup> suggested that if those with cardiovascular disease who dropped out of the trial were also cognitively impaired and had stayed in the trial, different, positive results of the intervention might have been detected.

### Summary of Evidence

Early trials treating patients with very high baseline BP suggested that lowering BP at these levels might be efficacious. However, issues related to the choice of outcomes relative to the age of the trial population, possible bias caused by sample attrition, and questions about quality control protocols raise the question of whether the hypothesis of cognitive benefit from BP

lowering has been adequately tested. Furthermore, bringing in new imaging-based outcomes to better understand the response to therapy and its relation to cognitive outcomes would enhance these trials. Trials recently ending should shed more light on this question. One trial, the SPRINT trial (Systolic Blood Pressure Intervention Trial),<sup>270</sup> with target treatment goals for elevated BP ended early because of efficacy on the main cardiovascular events<sup>271</sup> but has extensive data on brain health. Results from SPRINT-MIND (SPRINT Memory and Cognition in Decreased Hypertension) will be available next year. In the interim, careful control of BP might be a reasonable course of action, taking into account age and comorbidities.

### **Hypertension Treatment Over the Life Course**

Managing BP to maintain cognitive health will likely require taking into account the complex relationship among BP, age, the presence of comorbidities, and antihypertensive therapy. In this section, we review available evidence that sheds light on the expected cognitive benefit of treating hypertension across the life course.

### **Treatment of Hypertension in Children and Adolescents**

Clinically apparent vascular disease rarely occurs in children and adolescents. However, preclinical risk factors for vascular disease such as hypertension appear to have become more prevalent in the past few decades.<sup>272–274</sup> The basis for this rise in pediatric hypertension is unclear but may be explained in part by an increase in the rate of obesity.<sup>275,276</sup>

Given the rarity of pediatric vascular events such as stroke, little evidence directly ties pediatric hypertension to subsequent vascular outcomes during childhood and adolescence. However, 3 factors implicate childhood hypertension in the subsequent development of adverse outcomes in adulthood. First, childhood and adolescent hypertension often continues into adulthood. Moderate correlations have been found between BP during childhood and BP years later,<sup>277,278</sup> which suggests that early-life hypertension will often persist into later life stages in which it is a well-established risk factor for vascular events and cognitive impairment. Second, prospective cohort studies have found associations between childhood vascular risk factors such as hypertension and the presence of subclinical atherosclerotic lesions on autopsies of study subjects who died in young adulthood as a result of accidental trauma.<sup>279,280</sup> Similarly, hypertension in early life has been linked to *in vivo* measures of vascular dysfunction such as left ventricular hypertrophy on echocardiogram and carotid intima-media thickness on ultrasound.<sup>281</sup> Such findings place childhood hypertension on the pathway to preclinical vascular dysfunction, which in turn has been strongly linked to clinical vascular events such as stroke and heart failure. This parallels the pathway seen with adult-onset hypertension. Finally, the childhood presence of metabolic syndrome, of which hypertension is an integral part, has been directly associated with clinical vascular outcomes in early adulthood.<sup>282</sup> Taken together, these findings indicate that hypertension in early life not only serves as a prelude to hypertension in adulthood but also has already begun to have insidious effects on the vascular

system that predispose to symptomatic vascular disease early in life. In addition, several small studies have raised the suggestion that elevated BP has immediate adverse implications for cognitive function even in childhood.<sup>283–285</sup>

No randomized, clinical trial has evaluated the effect of antihypertensive therapy on clinical outcomes or markers of end-organ damage in the pediatric population.<sup>286</sup> The considerations above provide a plausible rationale for carefully treating hypertension in children and adolescents in the hope of preventing vascular events and cognitive impairment in adulthood. However, several cautionary points apply. The long-term safety of pharmacological treatment in children's growth has not been studied.<sup>286</sup> This supports a preferential emphasis on lifestyle modification, especially weight loss, before resorting to pharmacological therapy. Furthermore, many children with hypertension no longer manifest elevated BP in adulthood.<sup>277,278</sup> This uncertainty about the long-term durability of childhood hypertension calls for continual reassessment of BP and whether pharmacological therapy is needed, especially in patients who have successfully lost weight.<sup>276</sup>

### **Treatment of Hypertension in Young Adults**

Most cases of hypertension in individuals <40 years of age involve isolated diastolic hypertension.<sup>287</sup> This often progresses to also involve systolic hypertension as patients enter middle age.<sup>288</sup> Furthermore, even across the fifth decade of life, a strong association remains between increasing DBP and cardiovascular events such as myocardial infarction.<sup>289</sup> This natural history argues for attempts to reduce BP even in young adults, especially in patients who manifest any evidence of end-organ injury. Across randomized trials of antihypertensive therapy, the relative benefits of treatment and of specific classes of drugs do not appear to vary on the basis of whether patients were >65 or <65 years of age.<sup>290</sup> However, randomized, clinical trials have not been performed to specifically assess the benefits of pharmacological treatment of hypertension in young adults. In this context, nonpharmacological measures may be an especially compelling first-line approach. The PREMIER trial enrolled 810 relatively young adults (mean age, 50 years) with stage 1 hypertension (mean BP,  $\approx$ 135/85 mmHg) who were not receiving antihypertensive therapy. Subjects were randomly enrolled to a brief session of advice about factors affecting BP or to 1 of 2 intensive behavioral interventions. At 6 months, the intensive interventions led to an  $\approx$ 4-mmHg reduction in SBP.<sup>291</sup> This suggests that intensive nonpharmacological interventions in young adulthood may prevent the onset of hypertension or at least may delay the need for pharmacological therapy until later in midlife.

### **Treatment of Hypertension in Midlife**

Numerous randomized, clinical trials in middle-aged populations have shown that antihypertensive therapy substantially decreases the risk of adverse cardiovascular events such as stroke.<sup>292–295</sup> Some of these trials included measures of cognition. As discussed in the Interaction With Other Risk Factors, Including Genetics section, trial results do not clearly support or refute a beneficial effect of antihypertensive therapy in preserving cognition.<sup>296–300</sup>

Furthermore, by midlife, hypertension often occurs in the context of other systemic vascular risk factors such as dyslipidemia, diabetes mellitus, obesity, a sedentary lifestyle, and exposure to tobacco and environmental pollutants. Recent evidence from a large, randomized, clinical trial suggests that an overarching strategy for modifying these vascular risk factors helps to preserve cognition in individuals in their 60s and 70s.<sup>301</sup>

Finally, both clinically overt stroke and silent brain infarcts appear to lie on the causal pathway to cognitive impairment,<sup>159,302,303</sup> so widespread adoption of antihypertensive therapy to prevent stroke is likely to also result in improvements in cognition over the long term. A recent comparison of cognitive outcomes between 2 successive cohorts of elderly subjects born about a decade apart demonstrated better cognition in the later-born cohort.<sup>304</sup> These findings follow several prior reports to the same effect. An analysis of long-term care surveys from the United States across the 1980s and 1990s first suggested a temporal decline in the prevalence of dementia.<sup>305</sup> This pattern was corroborated by a separate US population-based survey that found an  $\approx 5\%$  decrease in the prevalence of cognitive impairment between 1993 and 2002.<sup>306</sup> Similar patterns have been found in analyses from Sweden and England.<sup>307,308</sup> These secular trends may have been driven by less exposure to adverse environmental influences such as pollution and greater exposure to antihypertensive therapy. However, such ecological conclusions cannot be drawn without more detailed data (Hypertension and Cognition: Clinical Trials of BP Lowering).

Overall, although robust evidence is lacking to prove that antihypertensive therapy in middle age provides a cognitive benefit, such a benefit appears likely on the basis of the epidemiological considerations above. Given the expected burden of cognitive impairment and dementia in an aging population, this suggestion of benefit provides a strong rationale for randomized, clinical trials of antihypertensive therapy designed primarily to test the hypothesis that aggressive control of hypertension during middle age can delay cognitive decline in later life. Although antihypertensive therapy in midlife is already supported by evidence of its benefit in reducing clinical events such as stroke, more robust evidence of its role in cognition would have important implications for our understanding of the pathogenesis of dementia. The results of the ongoing SPRINT-MIND trial (Interaction With Other Risk Factors, Including Genetics section) may help shed light on this question.

### Treatment of Hypertension in Late Life

Randomized, clinical trials did not shed much light on whether antihypertensive treatment protects cognitive function (Interaction With Other Risk Factors, Including Genetics section), but this uncertainty has been especially important in the very elderly. As discussed above, this population was well represented in HYVET (mean age,  $\approx 84$  years),<sup>250</sup> but other randomized, clinical trials of antihypertensive therapy have enrolled few patients  $>80$  years of age.<sup>292–295</sup> Furthermore, several observational studies have found that low BP, particularly low DBP, is associated with cognitive and physical decline

in the elderly<sup>107,128,149,154,309–311</sup> (Hypertension and Cognition: Observational Studies section).

It is unclear whether the relationship between low BP and cognitive decline in late life reflects a dysfunctional autonomic nervous system resulting in low BP, low BP leading to progressive hypoperfusion and brain atrophy, or some combination of these and other factors. Clearly, much more research is needed on the complex relationships among BP, antihypertensive treatment, frailty and multimorbidity, and cognitive and functional status in the oldest old. In the meantime, it may be reasonable to consider frailty and multimorbidity as a factor in decisions about antihypertensive therapy in late life. This is especially the case in patients who manifest intolerance of antihypertensive therapy in the form of symptoms such as orthostatic hypotension.<sup>312</sup> On the other hand, the results of the recently completed SPRINT trial, which included the oldest old, support the hypothesis that pharmacological treatment of elevated SBP reduces the risk of stroke and could help preserve cognition. The hope is that more detailed subgroup analyses of this age group will shed more light on the risks and benefits of antihypertensive treatment in the oldest old.

It is possible that better treatment of vascular risk factors earlier in life will reduce the prevalence of frailty in late life. Aging is associated with a progressive increase in SBP that occurs in the setting of stiffening of the arterial system<sup>313</sup> (Effects of Hypertension on Cerebrovascular Structure and Function section). Indirect evidence suggests that aggressive treatment of early-life and midlife vascular risk factors may retard the progression of these pathological changes. Caloric restriction, low-sodium diet, increased levels of exercise, and low exposure to hypertension have all been associated with less arterial stiffening.<sup>314–318</sup> If this is the case, then early treatment of hypertension and other vascular risk factors may both lessen the need for antihypertensive therapy and increase its safety in late life.

### Summary of Evidence

Direct evidence from randomized, clinical trials does not allow conclusive recommendations about treating hypertension throughout the life span to protect cognition. Observational studies suggest that hypertension causes an accumulating burden of vascular injury across all stages of life, but paradoxically, the end stages of vascular disease in frail elderly patients may be marked by low BP. Such considerations support the use of antihypertensive therapy throughout middle age and then continued efforts at judicious control of BP in elderly patients who appear likely to tolerate it. Results of randomized, clinical trials are awaited to prove the likely hypothesis that good control of BP and other vascular risk factors across the life span will help to stem the tide of cognitive impairment and dementia that would otherwise be expected with a continually aging population.

### Overall Summary and Future Directions

We have provided a broad overview of the cognitive impact of chronic hypertension. Hypertension disrupts the structure of cerebral blood vessels, promotes atherosclerosis, and impairs vital cerebrovascular regulatory mechanisms. These vascular changes increase the susceptibility of the brain to ischemic

injury, especially in vulnerable white matter regions critical for cognitive function, and may promote AD pathology. The evidence to date points strongly to a deleterious influence of midlife hypertension on cognitive function in midlife and late life. Executive function and processing speed seem to be the cognitive domains most affected, but memory can also be impaired. Therefore, it can be difficult to differentiate VCI from AD solely on the basis of the neurocognitive deficits. Although the data are not conclusive, there is evidence of an association between higher late-life BP and better cognition, highlighting the complexities of recommending uniform levels of BP across the life course. In addition to aging, menopausal status, *APOE*  $\epsilon$ 4 genotype, insulin resistance, systemic inflammation, and other comorbidities may potentiate the cognitive decline in individuals with hypertension.

Less clear are the effects of hypertension treatment on cognitive function. Observational studies have demonstrated a cumulative effect of hypertension on cerebrovascular damage, but evidence from randomized, double-blind, clinical trials that treatment of high BP at any stage over the life course improves cognition is far from conclusive. An intriguing relationship has emerged between hypertension and AD, raising the prospect that a chronic elevation in BP aggravates AD pathology, contributing to dementia. These findings are critically important because they raise the possibility that treatment of hypertension may also contribute to reduce the development or progression AD. Because no evidence-based recommendations can be made at this time, treatment of high BP in midlife and judicious use of antihypertensives in late life, taking into account cerebrovascular status and comorbidities, seem justified.<sup>3</sup>

Our analysis of the evidence also revealed a number of knowledge gaps that need to be addressed to gain a better understanding of the pathobiology and clinical impact of hypertension and to develop preventive and therapeutic strategies. One of the most promising aspects of an association between hypertension and dementia, including AD, is the prospect of prevention or early treatment as a strategy to reduce downstream cognitive impairment. Indeed, given how prevalent hypertension is and that there are many accessible and effective drugs, treatment of hypertension may prove to be one of the best ways to prevent or delay dementia. However, numerous questions and caveats remain. These are considered next.

How hypertension acts on cerebral arteries, the microcirculation, and other cellular elements in the neurovascular unit to produce changes in structure and function has not been fully elucidated. As we gain a better understanding of how the cells of the neurovascular unit and elsewhere interact to regulate cerebrovascular homeostasis and BBB permeability in the normal state, studies should also probe how hypertension interferes with the signaling pathways regulating such interactions in different districts of the cerebrovascular tree. The resulting knowledge may provide insight into the regional susceptibility of cerebral vessels to the effects of hypertension, that is, subcortical white matter and basal ganglia. The relative impact of the neurohumoral signals driving the elevation in BP and the mechanical forces acting on the vessel walls to induce changes in vascular cells and the extracellular

matrix need to be explored further. While elucidating how hypertension may lead to brain damage, these investigations could point to new therapeutic targets to prevent or ameliorate the deleterious effect of hypertension on the brain and may unveil class-specific effects on pathological processes driving cognitive impairment. Better use of available models and new experimental models that more closely reflect chronic hypertension in humans may be needed to generate translationally relevant results.

A key question concerns how the structural and functional effects of hypertension on the brain lead to cognitive impairment. WMHs and other brain lesions produced by SVD could reduce the connectivity, speed, timing, and spatial precision of the communication among brain regions critical for cognition (eg, the prefrontal cortex, cingulate cortex, and sensory regions), leading to psychomotor slowing and executive dysfunction.<sup>27</sup> On the other hand, hypoperfusion and reduced neurovascular coupling could induce brain dysfunction by depriving the energy-demanding regions involved in cognition of oxygen and glucose.<sup>319</sup> Hypertension-induced amyloid production and deposition could also play a role by promoting AD pathology. In the long run, whole brain and hippocampal atrophy are also likely to contribute by further reducing the processing power of the brain. Although these mechanisms are all plausible, supporting human data on their relative impact throughout the life course are lacking. Studies using connectomic-based approaches to investigate how hypertension affects brain networks in the presence or absence of structural damage (WMHs, silent strokes, etc) are now feasible and could provide new mechanistic insights. In addition, brain imaging approaches to investigate the relationship among CBF, cerebral energy metabolism, BBB permeability, and amyloid deposition could clarify the interaction among these different pathogenic factors and provide new biomarkers for risk assessment and early disease identification.

Whether treatment as early in the life course as possible, for example, hypertension in adolescence, would offer advantages for dementia prevention or pose too many side effects or other risks that would offset early and aggressive treatment is a critical question. This is particularly a concern at the extremes of the life span. It may be that childhood or early adulthood treatment is not cost-effective or the side effects outweigh the advantages. Similarly, in very late life, aggressive treatment may be more problematic than helpful. Although it is challenging to conduct a trial that covers much of the life span, adding sensitive and state-of-the-art cognitive outcomes to ongoing hypertension studies would be cost-effective and highly informative. Furthermore, advanced statistical methods could be applied to existing data sets to gain additional insight and to help better plan future trials. Trials should also include biomarkers of AD and other dementias because they may be helpful surrogate markers and may suggest new ways to identify hypertensive individuals at increased risk for cognitive impairment.

Related questions pertain to the trajectory of the cognitive decline in the hypertensive population and to the factors determining vulnerability. Although cognitive impairment is well documented in people with hypertension, little is known about the temporal dynamics of cognitive change in this population.



Prospective studies documenting the rate and timing of cognitive changes and identifying factors that may predict cognitive decline, for example, adherence to BP medication regimens or BP control and development of other comorbidities, would be highly relevant. Furthermore, in the AD and diabetic populations, brain changes may occur decades before cognitive changes.<sup>320,321</sup> It is unknown when the brain is most vulnerable to the deleterious effects of hypertension. Prospective studies that use state-of-the-art neuroimaging techniques and prehypertension samples would provide valuable insight into this brain-behavior relationship.

The effects of other comorbid illnesses, that is, clusters of comorbidities that combined with hypertension may have a greater cognitive impact, remain to be defined. It is well documented that multiple chronic illnesses, for example, diabetes mellitus, renal insufficiency/failure, and heart failure, are associated with cognitive impairment.<sup>3</sup> Furthermore, 3 of 4 individuals >65 years of age suffer from  $\geq 2$  chronic illnesses (ie, multimorbidity).<sup>322</sup> No research to date has examined the effect of multimorbidity on cognition; therefore, future studies should be designed around novel analysis techniques (eg, latent class analysis) to explore whether certain clusters of chronic illnesses are more predictive of cognitive impairment.

The cognitive tests that are most sensitive to changes in cognition across the life course also remain to be defined. As documented in this statement, cognitive tests vary dramatically between studies, making comparison of findings across studies difficult. Furthermore, the most commonly used instrument, the MMSE, is a measure of global cognition and is not as sensitive to subtle but clinically significant changes in cognition as domain-specific measures.<sup>323</sup> Given the inconsistency in cognitive measures, it is difficult to determine which neuropsychological tests are most sensitive to the cognitive changes that occur within the hypertensive population. Studies to document the psychometric properties of comprehensive neuropsychological batteries are needed to better determine which cognitive measures are most sensitive in hypertension across the life span.

Although some studies provided hints that certain classes of antihypertensive drugs may be more effective at improving cognition or lowering cognitive decline, most of these studies were underpowered or without equivalent cognitive end points. To better guide treatment, much more information will be needed on class of drugs and possibly how the efficacy of drugs may differ by sex and ethnicity. Future trials should ensure a diverse population that is large enough to detect the efficacy of drugs on subpopulations and ensure that more uniform cognitive outcomes are used. The question of the differential effect of treating SBP versus DBP is also understudied and has important clinical implications for risk assessment.

Furthermore, although the preponderance of evidence suggests that hypertension, especially at midlife, is a risk

factor for late-life cognitive impairment and dementia, several fundamental issues remain unanswered. Among these is how hypertension interacts with key pathogenic factors involved in neurodegeneration such as tau and A $\beta$  in promoting neurodegenerative disease.<sup>44,45</sup> The complicated interplay between cerebrovascular dysfunction and the production and clearance of these proteins through transvascular, perivascular, and paravascular pathways<sup>324,325</sup> is an important area for further investigation. The role of the dural lymphatics<sup>326</sup> in these clearance processes and the impact that hypertension has on lymphatic drainage remain to be assessed. These investigations may help address the role of hypertension in the alterations in amyloid trafficking observed in AD and in the evolution of neurodegeneration. With the advent of new neuroimaging techniques, especially amyloid and tau imaging, and biomarkers that can track preclinical disease, it may be possible to assess these interactions more readily.

In summary, basic, clinical, and neuropathological investigations have made remarkable progress in improving the understanding of the effect of hypertension on the brain vasculature and cognitive health, but much remains to be learned. Although there is substantial evidence that hypertension leads to cognitive impairment, an effect attributed to oxidative stress-driven cerebrovascular dysfunction and damage, the underlying cellular and molecular mechanisms remain incompletely understood. In addition, a critically important question still unanswered is whether treating hypertension prevents or reverses cognitive decline. Whereas difficulties in carrying on longitudinal studies for decades have played a role, the lack of appropriate and uniform cognitive outcomes across studies has also been a complicating factor. A complex relationship of hypertension with ethnicity, age, sex, and cerebrovascular risk factors has emerged, making it difficult to assess treatment effectiveness. The upcoming release of the results of the SPRINT-MIND trial may help fill some of these knowledge gaps. Despite numerous outstanding questions and caveats, personalized treatment of hypertension, taking into account age, sex, *APOE* genotype, metabolic traits, comorbidities, etc, remains a most promising and eminently feasible approach to safeguard vascular health and, as a consequence, brain health. Antihypertensive drugs are generally safe and widely available, but there is still much to be learned about how to best use them over the life course in the presence of comorbidities and whether specific classes of drugs may confer cognitive benefits beyond BP lowering. New discoveries in the cellular and molecular pathology of the cerebrovascular tree and associated cells, coupled with the use of new imaging tools, biomarkers, and genomic-proteomic approaches in clinical trials, offer the prospect to address these unanswered questions and to develop new treatments to mitigate the devastating impact of hypertension on cognitive health.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be “significant” if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person’s gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

\*Modest.

†Significant.

‡Dr Saczynski is now at Northeastern University.

### Reviewer Disclosures

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\*Modest.

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