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Blood Pressure and Cognitive Outcome

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Abstract Dementia, including Alzheimer's disease, vascular dementia, and "mixed" dementia, increases with age, yet its causes, particularly of Alzheimer's disease, are not well understood. Hypertension is an important risk factor for arteriosclerosis, particularly in the brain and kidney, and cardiovascular events, including stroke, which are risk factors for vascular dementia. Several excellent reviews have summarized the strong, consistent evidence that elevated mid-life blood pressure and hypertension are associated with higher risk of dementia and cognitive decline. However, several questions remain, including whether the relationship of blood pressure to cognitive outcomes changes with age, and whether antihypertensive medication use delays or prevents cognitive decline and dementia. The purpose of this article is to provide an update based on review of recent scientific reports and to highlight factors that might explain existing results and future research directions.

Keywords Blood pressure · Hypertension · Cognitive outcomes · Dementia

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Introduction

The prevalence of dementia increases with age so that more than 40% of the population ≥85 years of age may have clinical dementia [1]. About two thirds of dementia cases are attributed to Alzheimer's disease (AD) [1], for which the "causes," other than genetic factors such as apolipoprotein E_4, are undetermined [1]. Traditionally, AD was considered a neurodegenerative disease, distinct from dementia from vascular causes (VaD). However, it has become clear that there is a great deal of overlap between VaD and AD [2••]. The burden of cognitive impairment and dementia will increase with the continued aging of the population. Hypertension increases the risk of arteriosclerosis, particularly in the brain and kidney, and is an important risk factor for stroke and other cardiovascular events, which in turn are risk factors for VaD [2••]. However, there are several outstanding questions regarding the relationship between blood pressure (BP) and cognitive outcomes, including whether the relationship of BP to cognitive outcomes changes with age and whether antihypertensive medication use delays or prevents cognitive decline and dementia.

Does the Relationship of Blood Pressure to Cognitive Outcomes Change With Age?

Several excellent reviews have summarized the strong, consistent evidence that elevated mid-life BP and hypertension increases risk for dementia and cognitive decline [2••, 3, 4]. The relationship is less clear at older ages, where several studies have described an inverse relationship (i.e., lower BP is associated with dementia), or increased dementia or cognitive decline at both high and low levels

of BP [2••, 3, 4]. This J-curve was shown in a recent report that combined longitudinal observational data from the Rotterdam Study and the Leiden 85-Plus Study [5]. Relating higher systolic BP (SBP) and diastolic BP (DBP) to cognitive function 11 years later, Euser et al. [5] found that among those aged 65–74 years at baseline, higher baseline SBP and DBP predicted *worse* cognitive function at follow-up among those 65–74 at baseline, but *better* cognitive function among those aged >75 years at baseline.

The changing relationship of BP to cognitive outcomes with age was demonstrated by another recent report which analyzed the relationship of BP to incident dementia among men in the Honolulu Heart Project/Honolulu-Asia Aging Study over 32 years of follow-up [6•]. Compared with men who did not develop dementia (n=1,778), men who eventually developed dementia (n=112) had a greater increase in SBP from mid-life to late life (0.26 mm Hg per year), then a greater decrease in SBP (−1.36 mm Hg per year) [6•]. The declining SBP was observed over an approximately 6-year period prior to dementia diagnosis [6•]. These trends were attenuated with use of antihypertensive medication. A similar relationship was seen with DBP but only for VaD, and it was not modified by antihypertensive medication [6•].

Studies that found an increased risk of dementia or cognitive decline with low BP typically measured BP at older ages and had relatively short follow-up. The decline in BP prior to dementia incidence has been previously described, and a similar pattern is seen with body mass index and some other risk factors, and may be due to "wasting" or sarcopenia [3]. However, it is also possible that dementia-related brain changes directly affect BP regulation [3]. A recent observational study of AD patients reported that antihypertensive medication use was associated with slower cognitive decline [7], which suggests that lower BP is a consequence or correlate of the prodromal dementia state, and not a cause. The relationship between low BP and cognitive decline/dementia among older adults may also be due to survivor bias, where those with the highest levels of risk factors have died or had the outcome (so are excluded) prior to study baseline. The Leiden 85-Plus Study illustrates the difficulty in studying participants at these older ages, as it experienced greater than 50% dropout over 5 years, with 87.5% due to death and 12.5% due to refusal to participate [5]. This may contribute to reversal of relationships as noted with smoking, which like many other risk factors (body mass index, lipids) shows a paradoxical inverse relationship with cognitive decline and dementia at older ages [8]. A recent article emphasized the inherent bias of increased and selective loss to follow-up caused by death and cognitive decline [9, 10]. The appropriate analysis of such highly censored data with high levels of competing risks is an area of great interest.

Low BP may be causally related to cognitive outcomes through cerebral hypoperfusion. Cerebral autoregulation regulates cerebral blood flow (CBF) to maintain it within a narrow range, to prevent cerebral microvasculature damage. Lucas et al. [11•] recently tested the decades-old belief that CBF is independent of changes in mean arterial pressure (MAP) in a range of 60–150 mm Hg. They found that cerebral perfusion and oxygenation among healthy humans are affected by BP, and that CBF closely follows pharmacologic changes in BP [11•]. Interestingly, during hypotension, cerebral oxygenation increased compensatorily, whereas it decreased with hypertension, at a magnitude consistent with potential ischemic effects, indicating that hypertension could contribute to cerebral ischemia [11•]. Other recent studies have shown that patterns of regional CBF (rCBF) are altered in AD [12] and predict cognitive decline [13]. rCBF is also decreased in hypertensive individuals [14, 15] and improves with antihypertensive treatment [14].

Can Antihypertensive Medication Use Delay or Prevent Cognitive Decline and/or Dementia?

The observational Rotterdam Study recently reported a reduction in dementia incidence with use of antihypertensive medications [16]. The reduction was greater among those aged ≤75 years versus older than 75 years (8% vs. 4% per year). Likewise, two recent autopsy studies showed more AD pathology [17] and microinfarcts [18] among untreated hypertensive individuals compared with treated hypertensive individuals or normotensive individuals. The benefit of antihypertensive medication on cognitive outcomes in observational cross-sectional and longitudinal studies has been summarized in several excellent reviews [2••, 19, 20]. Of particular interest, Birns et al. [19] demonstrate that effects of BP lowering may differ across cognitive domains.

Randomized clinical trials (RCTs) of antihypertensive medications have shown relatively little benefit in preventing dementia, as summarized in a recent Cochrane review [21]. The Systolic Hypertension in Europe (Syst-Eur) trial showed a significant reduction in the incidence of dementia over both 2 and 4 years of follow-up [20]. However, other RCTs, such as the Study on Cognition and Prognosis in the Elderly (SCOPE), Systolic Hypertension in the Elderly (SHEP), Hypertension in the Very Elderly Cognitive Function Assessment (HyVET-Cog), and Protection against Recurrent Stroke Study (PROGRESS) did not find a significant difference in dementia by hypertension treatment [2••, 20]. The Cochrane reviewers acknowledge that the study results are difficult to interpret due to large numbers of participants who were lost to follow-up and

high numbers of placebo patients receiving active treatment. It is interesting that discontinuation rates among active participants were the lowest in Syst-Eur, the trial which showed a significant treatment benefit [21]. The HyVET study compared a diuretic plus an angiotensin-converting enzyme inhibitor (ACEI) with placebo among hypertensive individuals (SBP: 160–200 mm Hg, DBP<110 mm Hg) aged ≥80 years. HyVET was stopped early when interim analyses showed a significant reduction in stroke and total mortality [22]. HyVET-Cog failed to show a significant decrease in dementia [23], but in a meta-analysis of existing studies, the HyVET investigators reported a pooled relative risk of 0.87 (95% CI, 0.76–1.00; P=0.045). This meta-analysis differed from the Cochrane review in several methodologic choices, including which studies it included or excluded (e.g., it excluded the SCOPE study results because 84% of its placebo group took antihypertensive medications) [23]. The HyVET results demonstrated a benefit of treating hypertension among octogenarians, with no evidence that treatment increased dementia or cognitive decline. However, given that treated (mean) BP levels were about 140/80 mm Hg [22], these results cannot be extrapolated to the reduction of SBP to less than 140 mm Hg among adults aged ≥80 years.

It is possible that the antihypertensive effects on dementia seen in RCTs should be evaluated according to type of antihypertensive medication. In this view, superior cerebroprotection would occur with arterial dilating drugs (ACEIs, angiotensin receptor blockers [ARBs], and calcium channel blockers [CCBs]) due to their ability to reduce arterial wave reflections and central pressure pulsatility (PP) more than peripheral PP, and therefore reduce pressure pulsatility, which contributes to microvascular cerebral damage [24••]. Others argue that blocking the renin-angiotensin system is most important for cerebroprotection. Staessen et al. [2••] report a pooled odds ratio (OR) of 0.75 (95% CI, 0.60–0.94; P<0.01) for the three trials that started active treatment with renin inhibition (SHEP, Syst-Eur, and the combination arm of PROGRESS), and a pooled OR of 1.08 (95% CI, 0.84–1.38; P=0.54) for SCOPE (ARB) and the perindopril (ACEI)-only arm of PROGRESS. Syst-Eur, which found a significant treatment effect on dementia, was the only one to use a CCB (nitrendipine.) The hypothesis that use of centrally active ACEI (i.e., able to cross the blood-brain barrier) would be associated with decreased incidence of dementia was tested by Sink et al. [25], using longitudinal observational data from the Cardiovascular Health Study. Although overall ACEI use was not associated with dementia or cognitive decline, the use of centrally active ACEIs was associated with 65% less decline in Mini-Mental State Examination scores per year of exposure [25].

The failure to demonstrate significant reductions in dementia incidence in the RCTs may also be due to inadequate follow-up time, particularly given that several of the studies were stopped early due to significant effects on their primary cardiovascular disease end points at interim analysis. The follow-up time is likely too short to account for the long incubation period for dementia development. For example, data show blood pressure changes occur 6 years or more before incidence of dementia [6•]. Subclinical brain and vascular disease also develop over a long incubation period and may be important intermediaries between hypertension and cognitive outcomes, as reviewed below.

Potential Mechanisms for Relationship Between Blood Pressure and Cognitive Outcomes

With the advent of MRI, much has been learned about the relationship of cognitive outcomes to subclinical brain disease, including small vessel disease, as reflected by white matter hyperintensities (WMH) or white matter lesions (WML), and brain region size or cerebral atrophy. These MRI structural measures have proven to be powerful predictors of dementia and cognitive decline in longitudinal studies [26•, 27], and a recent report showed that worsening of white matter disease (WMD) over 3 years predicted incident dementia [28•].

There is also strong evidence that hypertension is a risk factor for increased WMH and atrophy, and that antihypertensive medication use is associated with less subclinical brain disease. Longitudinal data from 1,424 women aged ≥65 years in the Women's Health Initiative Memory Study (WHIMS) demonstrate an association between baseline hypertension with higher WML (more small vessel disease) at 8 years of follow-up [29]. WML volumes were highest among women who were treated but not controlled [29]. A recent longitudinal report from the Atherosclerosis Risk in Communities (ARIC) study found that cumulative SBP predicts worsening of WMH [30]. Finally, antihypertensive medication can reduce WMH, as demonstrated in active-treatment groups versus placebo groups in MRI substudies of both PROGRESS and SCOPE [31, 32].

Macrovascular disease may be another important mediator of the association between BP and cognitive decline. Stroke and cardiovascular disease (CVD) predict cognitive decline and dementia [33, 34]. Cognitive outcomes and WMD are also associated with subclinical atherosclerosis as measured by coronary artery calcification [35] and carotid intima-media thickness (IMT) and stenosis [36]. A novel mechanism for the association with IMT was shown in a recent report from the Baltimore Longitudinal Study of Aging, which found that patterns of resting cerebral blood

flow in older adults without clinical cerebrovascular disease were related to differences in carotid IMT [37]. Finally, the relationship of BP to cognitive outcomes may also be due to association with other dementia risk factors, particularly type 2 diabetes, lipids, physical activity, and insulin resistance [20].

The role of large artery stiffness in microvascular disease in target organs (e.g., brain and kidney) is increasingly recognized [24••]. Stiffening of the aorta and other large elastic arteries is usually measured via carotid-femoral pulse wave velocity, which is the gold-standard noninvasive index of large artery stiffening. Large artery stiffness is associated with older age, hypertension, type 2 diabetes, and kidney disease, and is also strongly associated with macrovascular outcomes and total mortality [24••]. Large artery stiffness directly reduces the ability of the aorta to "cushion" pressure changes with each heart contraction, resulting in increased pressure pulsatility [24••]. Large artery stiffness also contributes to mismatch between the vasculature and target organs (brain, heart, kidney, and eye) by increasing the speed with which pulse waveforms are reflected back from peripheral vasculature toward the aorta. The reflected waves, returning earlier during the cardiac cycle, merge with the primary outgoing pressure waveform such that they augment systolic pressure and fail to augment diastolic pressure. The result is widening pulse pressure and the development of isolated systolic hypertension [24••]. Recent reports have shown that arterial stiffness predicts cognitive outcomes in longitudinal studies [38, 39]. The microvasculature (e.g., in the brain, kidney, and eye) is particularly vulnerable to endothelial damage from this increased pressure pulsatility [24••]. Albuminuria, a marker of microvascular damage to the kidney, predicts a faster rate of cognitive decline [40], and microalbuminuria is associated with WMH (brain microvascular disease) [41, 42].

Future Research Directions

The relationship between BP and cognitive outcomes will be clarified by improved measurement, classification, and phenotyping of both 1) cognitive outcomes, including mild cognitive impairment [43] and dementia (AD vs. VaD) and their overlap [2••], and 2) blood pressure [24••].

Phenotyping of cognitive decline and dementia will improve with advances in imaging such as MRI, which has recently shown that the *microstructural* integrity of white matter is associated with gait variability [44] and cognitive function independently of *macrostructural* WMD (i.e., white matter atrophy and lesions) [45]. It has also recently become possible to noninvasively detect amyloid cerebral plaque deposition using positron emission tomography (PET) imaging and an amyloid-labeling PET ligand such as Pittsburgh Compound B (PIB). A recent study used serial PIB-PET imaging on healthy cognitively normal controls, individuals with amnestic mild cognitive impairment, and individuals with AD and found that cognitive decline was preceded and paralleled by neurodegeneration (i.e., MRI-measured cerebral atrophy) and that the cerebral amyloid deposition alone did not predict cognitive decline [46•]. Existing and new imaging modalities will not only allow for better phenotyping of dementia and cognitive impairment, but as noted by Petersen et al. [43], imaging is already being used to reduce the sample size for RCTs by stratifying on MRI volumetric indices.

Progress in the assessment of BP phenotypes may also be helpful in clarifying the relationship between BP and cognitive outcomes. A recent review article of the role of BP variability, instability, and episodic hypertension in predicting cardiovascular risk hypothesized that increased BP variability and instability are risk factors for vascular dementia [47•]. In fact, a relationship between mid-life SBP variability and late-life WML has previously been reported among men in the Honolulu-Asia Aging Study [48].

Recent antihypertensive RCTs, such as the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), have evaluated indices of arterial stiffness and/or arterial pulse wave analysis, and the role of central BP [24••]. Although highly correlated with BP and hypertension, arterial stiffness is increasingly recognized as a discrete entity that has multiple adverse effects related to the measurement and treatment of elevated BP. Arterial stiffness has also been shown to be a key predictor of SBP control in response to antihypertensive treatment [49••]. As previously noted, arterial stiffening reduces the ability of the aorta to cushion pulsatile pressure, increasing BP variability. This BP instability makes it more difficult to obtain accurate BP measurements for individuals with stiffer arteries, which is more common with age, diabetes, and renal disease. These individuals with stiff large arteries may be more susceptible to hypotension with antihypertensive treatment. This hypothesis was tested recently in a cross-sectional study of 9,985 hypertensive patients from the Veterans' Affairs system, showing that chronic kidney disease patients were at increased risk of diastolic hypotension with antihypertension medication [50].

Ambulatory blood pressure monitoring records 24-hour BP, which shows a predictable circadian rhythm of higher during the day, lower at night, and then increasing in the early morning prior to waking [51]. It can be used to diagnose white-coat hypertension or masked hypertension, and measurements may be more highly correlated with target organ damage [51]. In relation to cognitive outcomes, recent attention has focused both on the absolute level of night-time BP, and on variations from the classic "dipping" pattern, in which SBP declines overnight. Several small

studies have shown that an abnormal nocturnal pattern, such as non-dipping, extreme dipping, or increased nocturnal SBP, is associated with mild cognitive impairment [52], dementia [53], or brain atrophy [54].

Conclusions

More research is needed to clarify the relationship of BP to cognitive outcomes. There is strong evidence that controlling BP throughout life will prevent stroke and reduce the vascular damage that contributes to vascular dementia, and it may also reduce the incidence of AD. With regard to very elderly participants, the HyVET results demonstrated a clear reduction in stroke and mortality [22] and a trend toward reduced, rather than increased, dementia [23]. In meta-analysis, the clinical trials show a weak protective effect of antihypertension medication on cognitive function [23]. However, the target BP was less than 150/90 mm Hg, so HyVET does not answer the question of whether there is a risk in intensive BP reduction, particularly in the very elderly and others with high arterial stiffness. Clinical trial results are needed to test the hypotheses that ACEIs and ARBs are better at dementia prevention than CCBs or diuretics.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study has just published the results of its intensive BP-lowering arm, which showed that treating participants with type 2 diabetes and high CVD risk to a target BP of less than 120 mm Hg did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events [55•]. Both total and nonfatal stroke, a prespecified end point, were reduced, but the intensive BP group also experienced a higher rate of serious adverse events (3.3 vs. 1.3%; $P<0.001$) [55•]. A substudy, ACCORD–Memory in Diabetes (MIND), should provide valuable data regarding the positive or negative effect of intensive BP lowering on cognitive outcomes [56].

Future developments expected to clarify this research area are improved phenotyping of dementia and cognitive decline subtypes, brain imaging, hypertension subtypes, BP measurements (arterial stiffness, endothelial function, and pulse wave analysis), statistical analytic methods for evaluating competing risks in older cohorts, and trajectories in longitudinal data, which might demonstrate different phenotypes of decline.

While we await future progress, several points seem clear. Stroke is a major risk factor for dementia and cognitive decline [33]. Rates of stroke, other CVD events, and subclinical atherosclerosis are high among middle-aged and older adults, and antihypertensive medications are highly effective in reducing the incidence of stroke [51]. BP control rates remain poor [51]; therefore, current evidence supports increased attention to BP control as an important prevention measure for dementia and cognitive decline. Future clinical trials are needed to determine whether BP lowering will reduce risk of AD, and whether the risk reduction is affected by specific drugs or by prevention earlier in the process. Prevention of elevated BP throughout life, and thus the subsequent vascular brain changes, may have the single biggest effect on reducing the incidence of dementia.

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