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Editorial Commentary: Blood pressure and cognition in the elderly☆

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In this issue of the Journal, Goshgarian and Gorelick present a perspective on the current controversy regarding the relation of blood pressure and cognition in the elderly [1]. They discuss selected observational epidemiologic data and clinical trial studies that support or refute blood pressure lowering for preservation of cognition, potential underlying pathophysiology linking hypertension to cognitive impairment, current controversies regarding blood pressure management for possible cognitive preservation, and opportunities for future research. Their main conclusion is that although there is a plentitude of epidemiologic evidence relating blood pressure—both abnormally high and abnormally low to dementia rates, and biologically plausible mechanisms for hypertension-induced cognitive impairment, there is currently no answer to the question of whether or not lowering blood pressure with medications in older people will improve cognition or delay or attenuate declines in cognitive function, and more research is needed.

Both this conclusion and the evidence bear both greater scrutiny and consideration with respect to current preventive and therapeutic options for cognitive disorders.

Issue number one: Can we draw conclusions from the available data?

There are a number of reasons why the prior trials of hypertension treatment of older people that included measures of cognition in the study or a subset within the study (for detailed review of the six major studies see [2]) could fail to detect effects on cognitive function. They were of relatively short duration in relation to the time course of development of dementia (by design or early termination), cognitive assessment was unsophisticated and relatively insensitive (the mini-mental state examination [3] in SHEP [4,5], SYST-EUR [6,7], PROGRESS [8], SCOPE [9], HYVET [10,11], subset of MRC [12] or clinically recorded diagnoses of dementia (SYST-EUR) [6,7]), and sample sizes were not based on hypotheses related to cognitive changes.

Nonetheless, two of the six published high quality randomized hypertension treatment trials in older people (SYST-EUR (aged ≥60 years at entry [6,7], PROGRESS (mean age 64 year)) [8] detected significant benefits on either slowing cognitive decline or preventing dementia. A third reported a non-significant 16% reduction in dementia diagnosis in the antihypertensive treated group (SHEP [4,5], mean entry age 72 year). In a fourth (MRC [12], age entry criteria of 65–74 (mean 70.3 years)) initial results did not report a significant effect on cognition with abbreviated cognitive testing (paired associate learning tests(PALT) and trialmaking test part A (TMT)) [12]. A subset of subjects were retested with the MMSE after 9–12 years of antihypertensive treatment and better cognition was reported in those with greater lowering of systolic blood pressure [13]. A meta-analysis that combined data from both studies reporting positive effects on dementia development (SYST-EUR [6,7], PROGRESS (hypertension plus prior stroke or CVA) [8]) and those not initially reporting beneficial effects (SHEP [4,5] and HYVET [10,11]) concluded that there was a significant effect ($p = .045$) for the pooled ratio for reduced relative risk of dementia with treatment vs. placebo [11].

Of the 2 large randomized trials of hypertension that assessed cognition and did not detect effects on dementia rates or rates of cognitive decline, age requirement for entry was 80 years in HYVET and the trial was terminated early at 2.2 year with some participants receiving treatment for less than one year [10,11]. The other was initially designed as a placebo-controlled trial but allowed open label antihypertensive use (SCOPE) [9]. Mean enrollee age was 76 years and open label antihypertensive use was higher in the placebo-randomized than the treated group.

A consistent finding from all these randomized trials of hypertension treatment in older people is that none showed a decline in cognitive function despite varying target blood pressure entry criteria and targets, use of multiple classes of antihypertensive medications, and differing “older” age subgroups for enrollment.

Conclusion: There is an evidence base supporting positive effects on prevention of cognitive decline or development of dementia with initiation of treatment of hypertension in older people aged 60–75 years and no evidence for harmful effects on cognition in older people including those over 80 years.

Issue number two: Can we currently identify those older people most likely to have antihypertensive benefits on cognitive function with antihypertensive therapy.

There is great heterogeneity within older populations. Elderly people ranging from age 65 to 90 are not the same. Cardiovascular society statements have addressed differences in responses between patients older than 65 years, those 65–74 years, and those 75–84 years of age separately from those older than 85

☆ **Note**: New data have appeared since the initial submission of this communication. At the July 25, Alzheimer's Association International Conference (AAIC), SPRINT MIND results were reported. In 9361 hypertensive adults over the age of 50 with increased CVD risk but no diabetes or dementia at enrollment, treatment to a target systolic blood pressure goal of less than 120 mm Hg resulted in 15% fewer new cases of mild cognitive impairment compared to a target systolic blood pressure of less than 140 mm Hg. These results add to the compelling evidence for the treatment of hypertension to prevent cognitive decline.

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years of age [14–16]. Clinicians often separate older patients into two subgroups—those 65–80 years of age and those older than 80 years. As detailed above, the trial data mirror the epidemiologic data and appear to consistently show cognitive benefits of treating hypertension in middle-aged with vascular disease or elderly initiating anti-hypertensives at "younger" older ages up to 75. HY-VET suggests there is at least no harm in carefully selected patients over age 80.

Many factors affect cognition performance in elderly populations apart from neurodegenerative disorders, including education, vascular risk factors, psychiatric status, genetic background, hormonal changes, and use of certain medication classes (i.e. those with anticholinergic effects, hypnotic sedative drugs, opiates, and possibly proton pump inhibitors, among others). The epidemiological data suggest that the contribution of hypertension to development of dementia at older ages is strongest for those diagnosed with hypertension in mid-life to early old age (40–75 years) presumably based on longer exposure time for detrimental effects.

Emerging work with imaging and circulating biomarkers shows that there are abnormalities of many neural cells and elements years before cognitive changes occur and dementia of different etiologies may show abnormalities in different areas of the brain. [17–24] Neurocognitive testing in combination with clinical assessment with or without imaging can identify dementias due to Alzheimers disease, and deficits in subdomains most likely to progress from mild cognitive impairment to dementia [25–27]. These tools may improve the ability to identify people at risk for dementia and the ability to intervene before dementia is present.

Conclusion. While research to test the hypothesis that high risk people can be identified and treated to prevent cognitive decline with new modalities or medications is warranted, this is not relevant to the category of antihypertensive therapy as treatment of hypertension has unequivocally shown to have cardiovascular morbidity and mortality benefits.

Issue number three: Can other agents that affect CVD risk factors reduce the risk of cognitive decline in older people.

Reports on potential positive effects of statins on cognitive function are conflicting (data are reviewed in McGuinness et al. [28,29]). In older people with normal cognitive status at baseline, several but not all epidemiological and observational studies report protective effects of statin therapy on development of incident dementia and a slower rate of decline in cognitive function in older statin users compared to non-statin users assessed using a battery of neuropsychological tests. In two studies that analyzed results by age, beneficial effects were limited to those below age 80 years at enrollment [30,31].

A 2016 Cochrane review of two large placebo-controlled RCTs of statins to prevent dementia in 26,340 participants with or with risk factors for vascular disease (entry age 40–82 years, with 11,610 ≥70 years) [32], Trompet et al. [33] concluded although biologically feasible that statins could prevent dementia and initial evidence from observation studies was promising, there is good evidence that statins given in late life to people at risk of vascular disease do *not* prevent cognitive decline or dementia" [29].

Conclusion. Statins have not been shown to prevent cognitive decline or dementia in older people at risk of vascular disease.

Issue number 4: Ongoing and future research to improve cognitive function- where should the focus be?

Alzheimers disease (AD) accounts for about two thirds of cases of dementia and vascular dementia accounts for about 15–20%; thus reduction in CVD and CVD risk factors would only be predicted to target a minority of the people at risk for dementia. There is currently major investment in dementia research focused on Alzheimers disease and AD-related dementias. (National Alzheimers Project Act: https://aspe.hhs.gov/national-plans-address-alzheimers-disease; and the United Kingdom MRC initiative). There is unlikely to be future placebo-controlled randomized trials of blood pressure treatment in the elderly with the possible exception of trials in those over 80 years of age. Those over age 80, however, would be the least likely to show cognitive benefits. The SPRINT-MIND study may provide information on benefits of differing blood pressure targets on cognitive outcomes in those over 75 years of age. (www.sprinttrial.org) There will be additional data on statin effects on cognitive function in people over age 70 enrolled in a large randomized statin primary prevention of cardiovascular disease trial (STAREE: An ongoing clinical trial of statin therapy for reducing CVD events in the elderly; ClinicalTrials.gov NCT 02099123).

To summarize, there are no available therapies that can reverse cognitive deficits in patients with dementia despite attempts at developing drugs that target a number of pathways [34]. Thus, prevention is of the utmost importance and treatment of hypertension in older people may currently be the only proven effective approach. It is not only "reasonable" to treat hypertension as a strategy to lower the risk of cognitive decline, it should be advocated.

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