EDITORIAL

Prevention of Cognitive Impairment With Intensive Systolic Blood Pressure Control

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The prevalence of Alzheimer disease (AD) and related dementia is expected to triple over the next 30 years in the United States and worldwide.[1] Alzheimer disease drug development during the past 2 decades has met with disappointment. The last drug approved for this disease by the US Food and Drug Administration was in 2003 and was a drug with symptomatic, not disease-modifying, benefit. The challenges of drug development have been somewhat mitigated by advances in the determination of disease mechanisms, the identification of biomarkers and of genetic and nongenetic risk factors, and an updated conceptual framework for clinical development. In particular, an understanding that most neurodegenerative diseases take many years, if not decades, to develop and thus have a long preclinical phase has spurred interest in prevention. The identification of preclinical or early clinical phases, such as mild cognitive impairment (MCI), is critical for these primary and secondary prevention approaches.

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Increasingly, there has been recognition that risk factors could be modified during this preclinical course or even earlier in life. Several cardiovascular disease (CVD) risk factors, including diabetes and hypertension, have emerged as important risk factors for AD, in addition to vascular cognitive impairment.[2,3] The mechanisms by which CVD risk factors increase the risk of developing AD are most likely related to the important role in vascular health for β-amyloid and other neurodegenerative protein deposition and clearance.[2] Another factor may be the frequent co-occurrence of vascular pathology alongside neurodegenerative disease pathology and their interactive effect on clinical presentation.[4] Many observational studies have suggested that hypertension is associated with an increased risk of all-cause dementia.[5] Given that hypertension is highly prevalent worldwide, the population attributable risk is quite large, although there is considerable controversy whether midlife hypertension or late-life hypertension contributes more.[6] Several randomized clinical trials of traditional hypertensive treatment on cognitive outcomes have had mixed results, but none have included careful adjudication of dementia and MCI nor have had lengthy follow-up.[5]

It is this context that frames the important results of the Systolic Blood Pressure Intervention Trial (SPRINT) Memory and Cognition in Decreased Hypertension (MIND) study, reported in this issue of *JAMA*.[7] This is the first trial that has demonstrated an effective strategy for prevention of age-related cognitive impairment. The parent SPRINT study enrolled almost 9400 participants (mean age, 68 years) with hypertension and at increased risk of CVD (but without stroke or diabetes) and randomized them to standard treatment (systolic blood pressure [SBP] goal, <140 mm Hg) or to intensive treatment (SBP goal, <120 mm Hg). In 2015, the SPRINT trial was stopped early for benefit on its primary outcome of CVD events and all-cause mortality.[8]

The SPRINT MIND study was designed as part of SPRINT, with all-cause adjudicated probable dementia as a primary outcome and MCI and the composite measure of any cognitive impairment (probable dementia or MCI) as secondary outcomes. The cognitive assessment and dementia adjudication continued for almost 3 years after the SPRINT trial ended as a cohort phase, for a mean total follow-up of almost 6 years. Patients assigned to the intensive treatment had a nonstatistically significant reduction in all-cause probable dementia (7.2 vs 8.6 cases per 1000 person-years; hazard ratio, 0.83; 95% CI, 0.67-1.04) and statistically significant reductions in the risk of developing MCI (14.6 vs 18.3 cases per 1000 person-years; hazard ratio, 0.81, 95% CI, 0.69-0.95) and the risk of combined cognitive impairment outcome (20.2 vs 24.1 cases per 1000 person-years; hazard ratio, 0.85; 95% CI, 0.74-0.97).

There are some challenges regarding how to apply the SPRINT MIND results in clinical practice. The early termination of the trial and the extended follow-up as a cohort blurs what the effect size might have been if the intervention had continued as planned. The magnitude of the effect of intensive SBP lowering might have been greater given that during the cohort phase, which lasted about as long as the intervention phase, the SBP differences between treatment groups declined (from 13 mm Hg to 6 mm Hg). In addition, key considerations of adverse events were not available as these events were no longer monitored after the intervention phase ended. In the initial report of the SPRINT trial, the intensive SBP-lowering group had more frequent orthostatic hypotension, syncope, electrolyte abnormalities, and acute renal failure. This information, along with an accurate effect size, is critical to weigh benefits of treatment with adverse outcomes, many of which may worsen cognition.

Furthermore, information necessary to compare the effects of classes of antihypertensive agents on cognitive outcomes is also not provided. SPRINT used a quasi-pragmatic approach with suggestions for treatment choice, but practitioners approached SBP control individually and most participants were taking multiple drugs. Although the study population in the SPRINT trial was quite diverse, there was limited power to address differential effect of treatment by race. A recent study reported that older black adults may show greater effects

of SBP control on cognitive outcomes.[9] This finding requires further investigation.

The SPRINT trial has already changed clinical care. It will be of great interest to watch how the results of SPRINT MIND influence approaches to maintaining brain health and preventing cognitive impairment. Critical questions will be when to treat elevated SBP and whether the same goal of care should be applied to adults of all ages. One group that deserves special consideration is the oldest old (traditionally defined as ≥85 years). Although a prespecified subgroup analysis was conducted for those aged 75 years or older vs those younger than 75 years and the main SPRINT results were also demonstrated among those aged 75 and older,[10] there is no information on how many participants were aged 80 years or older and if treatment effects might differ in these very old adults. Several observational studies have reported an inverse association of hypertension on the risk of dementia with a protective effect among the oldest old.[5] This may be partly explained by survival bias, but it is possible that higher perfusion pressure may be beneficial to brain health at that advanced age.[11] This is important given that the incidence of MCI and dementia continues to increase in very late life and adverse events from intensive BP control also increase. Because participants were excluded from SPRINT if they had diabetes, stroke, or symptomatic heart failure, the intensive SBP control approach used in this trial cannot be generalized to older adults with those conditions.

Another important but understudied group for BP control, both diastolic and systolic, is young adults (ie, aged <40 years). With the recent increase of CVD risk factor prevalence in children and young adults, even a high-normal SBP (such as 120-140 mm Hg) that may last for many decades could be detrimental to brain health. The Coronary Artery Risk Development in Young Adults (CARDIA) study reported that a higher burden of SBP elevation over 25 years from young adulthood to midlife was associated with worse performance on several cognitive tests in midlife (mean age, 50 years).[12] Trials, both pharmacological and behavioral, need to be conducted to determine if treatment (and level of treatment) earlier in life reduces later-life vascular events and cognitive impairment. Nonetheless, the connection between heart and vascular health and brain health is not appreciated by many patients and physicians, and it is essential to highlight this relationship in a public health campaign for people of all ages.

For older adults, almost all of whom have concern about being diagnosed with AD and related dementia, SPRINT MIND offers great hope. The study demonstrates that among those with hypertension, intensive SBP control can reduce the development of cognitive impairment. This approach should be studied with other vascular health interventions, such as physical activity and other promising approaches for prevention.[13] Indeed, the timing is right to investigate multidomain risk reduction strategies personalized for older adults and their individual risk profiles. Eventually this modifiable risk factor approach could be combined with disease-modifying drugs so that one day, it will be possible to identify persons at risk of AD and related dementia (either by biomarkers, genetics, or cognitive symptoms) and offer an effective strategy for prevention of cognitive impairment. The SPRINT MIND study may not be the final approach for prevention of AD or other cognitive impairment but it represents a major leap forward in what has emerged as a marathon journey.

ARTICLE INFORMATION

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