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A Link Between Cardiovascular Risk Management and Alzheimer Disease Is Still Elusive

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Alzheimer disease (AD) is the sixth leading cause of death in the US, but existing treatments provide only a modest improvement in symptoms. To our knowledge, no approved treatment exists that improves the course of disease or underlying pathology. Research on disease-modifying AD treatments has proven to be extremely challenging, with a number of major recent clinical trials of drug therapies resulting in negative or ambivalent findings.[1,2] While many alternative ideas for developing a treatment for AD are being pursued, 2 key strategies have emerged: initiating interventions earlier in the course of disease in individuals who are at risk but unimpaired and identifying targets beyond abnormal amyloid and tau proteins, the pathology that defines AD.

These strategies have been deployed in several recent interventions examining whether reduction of cardiovascular risk can lead to cognitive benefits in unimpaired older adults.[3,4] Cardiovascular risk factors, such as hypertension, are an appealing target for treatment because they appear to increase risk of diagnosis of dementia in addition to their well-established role in predicting cardiovascular outcomes like stroke and heart attack. However, there is no clear mechanism linking cardiovascular risk to AD.

One of these trials, the Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT MIND) study,[5] monitored 9361 individuals 50 years and older with hypertension but without diabetes or dementia for about 5 years. Intensive hypertension control (less than 120 mm Hg) was associated with lower rates of conversion to mild cognitive impairment (MCI) than standard control (less than 140mm Hg), but the interventions did not influence rates of conversion to AD alone. MCI is considered a precursor to AD because about 10% to 15% of individuals with MCI in clinical samples progress to clinically diagnosed AD per year, but some do not, or they progress to non-AD dementia.[6,7] This variability in clinical trajectory is broadly consistent with biomarker data in MCI. At least 30% to 35% of patients with MCI have negative amyloid positron emission tomographic results, indicating that non-AD etiologies account for clinical deficits in a substantial proportion of these individuals.[8,9] The fact that hypertension control in the SPRINT MIND study predominantly influenced MCI incidence in particular may have

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been due to insufficient follow-up time to see sufficient rates of conversion to AD in this unimpaired, relatively young sample, or it could be because the treatment targeted functional outcomes that overlap with MCI but are not specifically linked to the AD pathway. Thus, identification of underlying AD pathophysiology driving the decreased MCI incidence would be ground-breaking in that it would establish a definitive link between hypertension control and reduced risk of AD.

Nasrallah et al[10] enrolled a subset of 673 SPRINTMIND participants across 7 clinical sites to determine whether intensive hypertension treatment is associated with brain changes measured with longitudinal magnetic resonance imaging (MRI) at baseline and 4 years. The analysis included a total of 454 participants for whom longitudinal follow-up data were available. While amyloid and tau biomarkers were not available in this study, the investigators carefully selected a variety of MRI measurements optimized for detection of AD-sensitive neurodegeneration and white matter tract changes. The treatment groups did not differ in changes in blood flow, cortical volume, thickness of a set of regions susceptible to AD, or structural integrity of the cingulum bundle. Unexpectedly, however, the intensive treatment group had greater hippocampal atrophy than the standard treatment group, despite comparable group characteristics at baseline. As Nasrallah et al[10] note, the absence of amyloid and tau measurements limits definitive conclusions about the specificity of these findings to AD. However, the MRI results and the lack of an influence of intensive treatment on AD incidence in the main trial together do not support a role for hypertension control in mitigating AD risk.

Longitudinal imaging data in a large, rigorous multisite clinical trial like the SPRINT MIND study are valuable because they may be able to establish a causal link between hypertension and the brain whereas epidemiological data cannot. But given the complexity of these and other recently published SPRINT MIND findings, how confident can we be in ruling out the influence of hypertension control on AD-related brain changes? Differing subsample sizes and characteristics contribute to the challenge of interpreting findings across studies. For example, the MRI substudy sample of 454 individuals included only 5% of the participants of the main study, and reduced MCI incidence with intensive hypertension control reported in the main study was not replicated within this smaller group. Insufficient statistical power is a likely explanation, along with reported differences in the MRI subsample (younger, more likely to be female, less likely to be Hispanic, lower systolic blood pressure, higher cognitive function) compared with the larger SPRINT MIND sample. Such differences may have reduced the likelihood of detecting cognitive or brain changes in the smaller MRI subsample. The authors examined well-validated MRI biomarkers that perform well in differentiating AD from healthy controls, but it is unclear how much AD-related neurodegeneration would be expected in this relatively young and unimpaired group, since substantial neurodegeneration typically occurs later in the course of disease and in parallel with clinical impairment.[11]

Increased hippocampal atrophy in the intensive treatment group was the only intervention-related finding that met statistical significance in this study.[10] While counterintuitive, it is consistent with a recent report in the same SPRINT MIND sample of an intensive intervention-related association with another non-AD specific biomarker: decreased total

brain volume.[12] Furthermore, in recent results from the SPRINT MIND cognitive substudy of 2921 individuals, intensive hypertension control was linked to another negative outcome, worse longitudinal processing speed, but no improvement in any cognitive domain.[13] These findings raise similar questions about the statistical power and representativeness of this subsample vs the overall SPRINT MIND sample and the MRI subsample. It is also difficult to understand what mechanism related to intensive hypertension control might underlie worse processing speed or hippocampal and overall brain atrophy outcomes, and whether these findings together might limit enthusiasm for clinical use of this treatment in some individuals who are at higher risk of cognitive decline. On the other hand, at least one key intensive hypertension-related benefit has been reported in the MRI substudy sample: intensive hypertension treatment was linked to an attenuated increase in white matter lesion volume.[12] This parallels other hypertension treatment trials reporting treatment-related improvement in white matter abnormalities and points to a possible vascular mechanism underlying the clinical benefit of intensive hypertension control.[14–16] The recent Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial has also provided evidence that lifestyle changes, including cardiovascular risk factors modification, improve cognitive trajectories.[3]

The complex pattern of findings across multiple studies suggests that the mechanistic link between cardiovascular health and AD is still elusive. Intensive hypertension control was linked to some worse outcomes (eg, total brain and hippocampal volume decreases and poorer processing speed) and to some benefits (an improvement in white matter hyperintensities and reduced incidence of MCI), but intervention groups do not differ for most measures reported in the SPRINT MIND cognitive and MRI substudies. The fact that these associations were examined in different subsamples with varying representativeness of the main trial cohort adds to the complexity of interpretation. The findings of the SPRINT study overall suggest that the primary benefit of intensive hypertension control is in reducing cardiovascular events. But the SPRINT MIND data thus far do not point to a clear additional benefit of such treatment in maintaining cognitive function or reducing the risk of AD. Future work is needed to understand how AD and cerebrovascular pathophysiology contribute to the complex relationship between cardiovascular health and cognitive decline.

REFERENCES

1. Sperling R, Henley D, Aisen PS, et al. Findings of efficacy, safety, and biomarker outcomes of atabecestat in preclinical Alzheimer disease: a truncated randomized phase 2b/3 clinical trial. JAMA Neurol. Published online January 19, 2021. doi:10.1001/jamaneurol.2020.4857
2. Knopman DS, Jones DT, Greicius MD. Failure to demonstrate efficacy of aducanumab: an analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimer's Dement. Published online November 1, 2020.. doi:10.1002/alz.12213
3. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015;385(9984):2255–2263. doi:10.1016/S0140-6736(15)60461-5 [PubMed: 25771249]
4. Wright JT Jr, Williamson JD, Whelton PK, et al. ; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–2116. doi:10.1056/NEJMoa1511939 [PubMed: 26551272]

5. Williamson JD, Pajewski NM, Auchus AP, et al. ; SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. JAMA. 2019;321(6):553–561. doi:10.1001/jama.2018.21442 [PubMed: 30688979]
6. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. Arch Neurol. 2009;66(12):1447–1455. doi:10.1001/archneurol.2009.266 [PubMed: 20008648]
7. Farias ST, Mungas D, Reed BR, Harvey D, DeCarli C. Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. Arch Neurol. 2009;66(9):1151–1157. doi:10.1001/archneurol.2009.106 [PubMed: 19752306]
8. Landau SM, Horng A, Fero A, Jagust WJ; Alzheimer's Disease Neuroimaging Initiative. Amyloid negativity in patients with clinically diagnosed Alzheimer disease and MCI. Neurology. 2016;86(15):1377–1385. doi:10.1212/WNL.0000000000002576 [PubMed: 26968515]
9. Dickerson BC, Wolk DA; Alzheimer's Disease Neuroimaging Initiative. Biomarker-based prediction of progression in MCI: comparison of AD signature and hippocampal volume with spinal fluid amyloid-β and tau. Front Aging Neurosci. 2013;5:55. doi:10.3389/fnagi.2013.00055 [PubMed: 24130528]
10. Nasrallah IM, Gaussoin SA, Pomponio R, et al. ; SPRINT Research Group. Association of intensive vs standard blood pressure control with magnetic resonance imaging biomarkers of Alzheimer disease: secondary analysis of the SPRINT-MIND randomized trial. JAMA Neurol. Published online March 8, 2021. doi:10.1001/jamaneurol.2021.0178
11. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535–562. doi:10.1016/j.jalz.2018.02.018 [PubMed: 29653606]
12. Nasrallah IM, Pajewski NM, Auchus AP, et al. ; SPRINT MIND Investigators for the SPRINT Research Group. Association of intensive vs standard blood pressure control with cerebral white matter lesions. JAMA. 2019;322(6):524–534. doi:10.1001/jama.2019.10551 [PubMed: 31408137]
13. Rapp SR, Gaussoin SA, Sachs BC, et al. ; SPRINT Research Group. Effects of intensive versus standard blood pressure control on domain-specific cognitive function: a substudy of the SPRINT randomised controlled trial. Lancet Neurol. 2020;19(11):899–907. doi:10.1016/S1474-4422(20)30319-7 [PubMed: 33098800]
14. White WB, Wakefield DB, Moscufo N, et al. Effects of intensive versus standard ambulatory blood pressure control on cerebrovascular outcomes in older people (INFINITY). Circulation. 2019;140(20):1626–1635. doi:10.1161/CIRCULATIONAHA.119.041603 [PubMed: 31607143]
15. Dufouil C, Chalmers J, Coskun O, et al. ; PROGRESS MRI Substudy Investigators. Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) magnetic resonance imaging substudy. Circulation. 2005;112(11): 1644–1650. doi:10.1161/CIRCULATIONAHA.104.501163 [PubMed: 16145004]
16. de Havenon A, Majersik JJ, Tirschwell DL, McNally JS, Stoddard G, Rost NS. Blood pressure, glycemic control, and white matter hyperintensity progression in type 2 diabetics. Neurology. 2019;92(11):e1168–e1175. doi:10.1212/WNL.0000000000007093 [PubMed: 30737332]