Sprint Mind 2.0

By Michele G. Sullivan from JAMA

A new iteration of the SPRINT MIND hypertension trial will seek to prove conclusively the original study's tantalizing suggestion: that intensive blood pressure control decreases the risk of developing mild cognitive impairment (MCI) and, eventually, dementia. SPRINT MIND 2.0 will recruit SPRINT MIND subjects and enable another follow-up cognitive assessment and other clinical tests as they remain on their standard of care blood pressure regimen. It is largely funded by an $800,000 grant from the Alzheimer's Association.

Initially released last July at the Alzheimer's Association International Conference, the results of SPRINT MIND have now appeared on-line in JAMA. Although it failed to meet its primary end- point of reducing dementia incidence, the study did score on two secondary endpoints. Patients who reduced their systolic blood pressure to less than 120 mm Hg were 19% less likely to develop MCI and 17% less likely to be diagnosed with all-cause dementia than were those who achieved a hypertension target of less than 140 mm Hg.

The secondary results, and positive movement in the primary results, sparked excitement in the dementia research community last summer. They have suggested that" the median 5-year follow-up just wasn't long enough to show any significant effects on dementia, which can take years to fully manifest. Adding 2 more years with SPRINT MIND 2.0 should be long enough to discern those benefits, if indeed they exist.

"SPRINT MIND 2.0 and the work leading up to it offers genuine, concrete hope," Maria C. Carrillo, PhD, chief science officer for the Alzheimer's Association, said in a press statement. "MCI is a known risk factor for dementia, and everyone who experiences dementia passes through MCI. When you prevent new cases of MCI, you are preventing new cases of dementia. The Alzheimer's Association finds these data to be compelling and is committed to getting clarity and certainty on the dementia outcome by following participants for a longer period of time." The study strengthens the new and energetic push to find ways to prevent dementia, which has proven itself intractable in every drug study to date.

"This study is in line with where the field of dementia research is going: preventing memory loss earlier," said Laurie Ryan, PhD, chief of the dementias of aging branch in the National Institute on Aging. "Much like we have research-based interventions for heart health and cancer prevention, we hope to have guidance based on this and subsequent studies that will more definitively show how to slow or even stop dementia well be- fore symptoms appear."

NIA director Richard J. Hodes, MD, agreed.

"Dementia continues to be a large public health challenge, and based on the primary results of this study, we still have yet to find an intervention strategy proven to reduce the risk of dementia," he said in a press statement. "Nevertheless, the secondary results showing that intensive lowering of blood pressure may reduce risk for MCI, a known risk factor for dementia, give us additional avenues to explore on the path to prevention."

SPRINT MIND was a substudy of the Systolic Blood Pressure Intervention Trial (SPRINT). It compared two strategies for managing hypertension in older adults. The intensive strategy had a target of less than 120 mm Hg, while standard care had a target of less than 140 mm Hg. SPRINT showed that more intensive blood pressure control produced a 25% reduction in the composite primary composite endpoint of cardiovascular events, stroke, and cardiovascular death. The intensive arm was so successful that SPRINT helped inform the 2017 high blood pressure clinical guidelines from the American Heart Association and American College of Cardiology.

The SPRINT MIND substudy, headed by Jeff D. Williamson, MD, of Wake Forest University, Winston-Salem, N.C., asked whether intensive management had any effect on probable all-cause dementia or MCI, as well as imaging evidence of changes in white-matter lesions and brain volume. It followed patients for up to 7 years and comprised 9,361 SPRINT subjects at least 50 years old (mean, 68 years) with at least one cardiovascular risk factor. Nearly a third (30%) were black, and 10% Hispanic. The primary outcome was incident probable dementia. Secondary outcomes were MCI and a composite of MCI and/ or probable dementia. About a third had a systolic BP of 132 mm Hg or less, another third had a systolic pressure of 132-145 mm Hg, and the remainder had a systolic pressure greater than 145 mm Hg. Physicians could use their choice of antihypertensive treatments. The study protocol encouraged, but did not

mandate, thiazide-type diuretics as a first-line agent, followed by loop diuretics and beta-adrenergic blockers. Chlorthalidone was encouraged as the primary thiazide-type diuretic, and amlodipine as the preferred calcium channel blocker. The interventions did successfully control blood pressure, with a significant difference between the treatment groups. The mean systolic BP was 121.6 mm Hg in the intensive-therapy group and 134.8 mm Hg in the standard group—a statistically significant difference of 13.3 mmHg.

Dementia developed in 149 in the aggressive—control group and 176 in the standard group—a nonsignificant difference of 17% (hazard ratio, 0.83). MCI developed in 287 in the intensive group and 353 in the standard- treatment group. This amounted to a statistically significant 19% reduction. There was also a significant 15% reduction in the composite outcome of MCI or probable dementia in favor of intensive treatment. As evidenced by the Alzheimer's Association grant, dementia re- searchers chose to focus on SPRINT MIND's positive secondary end- points. At the AAIC meeting, Dr. Williamson even suggested that antihypertensive medications could be seen as disease—modifying agents for cognitive decline. Data support his claim: No dementia intervention yet tested has approached this level of success.

"I think we can say this is the first disease-modifying strategy to reduce the risk of MCI," Dr. Williamson said during a press briefing. And although the primary endpoint—the 17% relative risk reduction for probable all—cause dementia-didn't meet statistical significance, "It's comforting to see that the benefit went in the same direction and was of the same magnitude."

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VIEW ON THE NEWS

'Major leap forward' in AD prevention research

SPRINT MIND offers hope that a very achievable blood pressure goal can dramatically alter the trajectory from mild cognitive impairment to dementia, Kristine Yaffe, MD, wrote in an accompanying editorial. But at this point, it's impossible to make specific clinical recommendations.

"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 [systolic blood pressure] 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."

Additionally it is not possible, right now, to know which hypertension treatment regimens were most effective in improved cognitive outcomes.

"lnformation 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."

Nevertheless, the positive secondary findings and the encouraging trajectory on dementia risk should fix blood pressure management squarely into a cornerstone of dementia prevention algorithms.

"The SPRINT MIND study may not be the final approach for prevention of AD [Alzheimer's disease] or other cognitive impairment, but it represents a major leap forward in what has emerged as a marathon journey."

Dr. Yaffe is professor of psychiatry, neurology, and epidemiology and the Roy and Marie Scola Endowed Chair at the University of California, San Francisco.