JAMA | Original Investigation

Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia
A Randomized Clinical Trial

The SPRINT MIND Investigators for the SPRINT Research Group

IMPORTANCE There are currently no proven treatments to reduce the risk of mild cognitive impairment and dementia.

OBJECTIVE To evaluate the effect of intensive blood pressure control on risk of dementia.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted at 102 sites in the United States and Puerto Rico among adults aged 50 years or older with hypertension but without diabetes or history of stroke. Randomization began on November 8, 2010. The trial was stopped early for benefit on its primary outcome (a composite of cardiovascular events) and all-cause mortality on August 20, 2015. The final date for follow-up of cognitive outcomes was July 22, 2018.

INTERVENTIONS Participants were randomized to a systolic blood pressure goal of either less than 120 mm Hg (intensive treatment group; n = 4678) or less than 140 mm Hg (standard treatment group; n = 4683).

MAIN OUTCOMES AND MEASURES The primary cognitive outcome was occurrence of adjudicated probable dementia. Secondary cognitive outcomes included adjudicated mild cognitive impairment and a composite outcome of mild cognitive impairment or probable dementia.

RESULTS Among 9361 randomized participants (mean age, 67.9 years; 3332 women [35.6%]), 8563 (91.5%) completed at least 1 follow-up cognitive assessment. The median intervention period was 3.34 years. During a total median follow-up of 5.11 years, adjudicated probable dementia occurred in 149 participants in the intensive treatment group vs 176 in the standard treatment group (7.2 vs 8.6 cases per 1000 person-years; hazard ratio [HR], 0.83; 95% CI, 0.67-1.04). Intensive BP control significantly reduced the risk of mild cognitive impairment (14.6 vs 18.3 cases per 1000 person-years; HR, 0.81; 95% CI, 0.69-0.95) and the combined rate of mild cognitive impairment or probable dementia (20.2 vs 24.1 cases per 1000 person-years; HR, 0.85; 95% CI, 0.74-0.97).

CONCLUSIONS AND RELEVANCE Among ambulatory adults with hypertension, treating to a systolic blood pressure goal of less than 120 mm Hg compared with a goal of less than 140 mm Hg did not result in a significant reduction in the risk of probable dementia. Because of early study termination and fewer than expected cases of dementia, the study may have been underpowered for this end point.

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Visual Abstract

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Supplemental content

Authors/Group Information: The SPRINT MIND Investigators are listed at the end of this article. A list of the members of the SPRINT Research Group has been previously published.[13]

Corresponding Author: Jeff D. Williamson, MD, MHS, Section on Gerontology and Geriatric Medicine, Department of Internal Medicine, Sticht Center for Healthy Aging and Alzheimer's Prevention, Center for Healthcare Innovation, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157 (jwilliam@wakehealth.edu).

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Alzheimer disease and related dementias are projected to affect 115 million people worldwide by 2050.[1] To date, there are no proven interventions that prevent or delay the incidence of dementia or mild cognitive impairment (MCI), a clinical state between normal cognitive aging and dementia.[2] Hypertension, which affects more than 75% of persons older than 65 years,[3] has been identified as a potentially modifiable risk factor for MCI and dementia in observational studies.[4,5] Individuals with Alzheimer disease commonly exhibit features of vascular damage in combination with β-amyloid and tau neuropathology.[6-8] Randomized clinical trials of systolic blood pressure (SBP) reductions greater than 4 mm Hg that have included cognitive assessment have generally been inconclusive, but none, to our knowledge, have included a follow-up of longer than 4 years with expert adjudication of dementia and MCI.[9,10] Although no randomized clinical trial of SBP lowering has shown harm, some observational studies have identified an association between low BP and higher risk of cognitive impairment.[11,12]

The Systolic Blood Pressure Intervention Trial (SPRINT) was designed to test the effect of more intensive BP control on cardiovascular (primary end point), renal, and cognitive outcomes in persons without diabetes or preexisting stroke. Results for cardiovascular and renal outcomes have been previously reported.[13,14] This article describes the effect of intensive BP control (SBP target <120 mm Hg) on the rate of probable dementia and MCI compared with a standard SBP treatment goal of less than 140 mm Hg.

Key Points

Question Does intensive blood pressure control reduce the occurrence of dementia?

Findings In this randomized clinical trial that included 9361 adults with hypertension, randomization to a systolic blood pressure target of less than 120 mm Hg compared with less than 140 mm Hg resulted in a rate of probable dementia of 7.2 vs 8.6 cases per 1000 person-years, a difference that was not statistically significant.

Meaning Among adults with hypertension, intensive blood pressure control did not significantly reduce the risk of probable dementia.

Methods

Trial Design

The trial design and methods have been published previously,[13,15] and the study protocol is provided in Supplement 1. The study was approved by the institutional review board at each participating site, and each participant provided written informed consent. Briefly, we conducted a multicenter randomized clinical trial that compared 2 strategies for managing SBP in older adults with hypertension who were at increased risk of cardiovascular disease.

Participants were aged 50 years or older and had an SBP between 130 and 180 mm Hg at the screening visit. Participants were considered to have an increased cardiovascular risk if they had clinical or subclinical cardiovascular disease, chronic kidney disease (defined by an estimated glomerular filtration rate of <60 mL/min/1.73 m^2), or a Framingham Risk Score of 15% or greater or if they were aged 75 years or older. Individuals residing in a nursing home, persons with a diagnosis of dementia (based on medical record review), and those treated with medications primarily used for dementia therapy were excluded, as were persons with prevalent diabetes mellitus or history of stroke. Race and ethnicity were collected via self-report using fixed categories to satisfy the National Institutes of Health Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research.

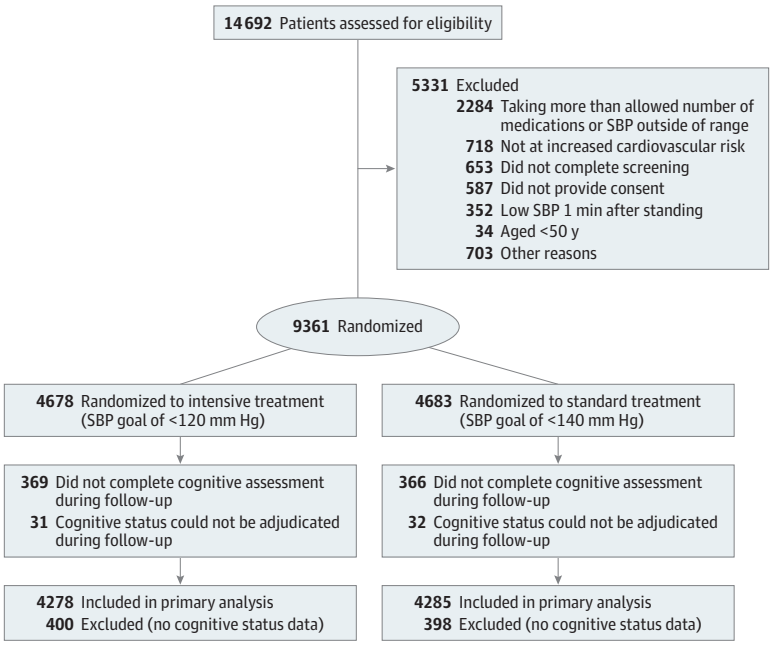
Individuals were randomized by the data coordinating center in a 1:1 ratio to either an SBP goal of less than 120 mm Hg (intensive treatment group; n = 4678) or an SBP goal of less than 140 mm Hg (standard treatment group; n = 4683). The randomization was stratified by clinic site. The algorithms and formulary for the trial are listed in the study protocol (Supplement 1). All major classes of antihypertensive agents were included in the formulary and were provided at no cost to participants. The protocol encouraged but did not mandate use of thiazide-type diuretics as a first-line agent, loop diuretics for participants with chronic kidney disease, and β-adrenergic blockers for participants with coronary artery disease.[16,17] Enrollment began on November 8, 2010, and ended in March 2013.

Ascertainment of Mild Cognitive Impairment and Probable Dementia

Ascertainment of cognitive status followed a 3-step process. In-person cognitive screening assessments were administered to all participants at baseline and during follow-up by centrally trained and certified examiners at each local site and included a test of global cognitive function (Montreal Cognitive Assessment [MoCA]; range, 0-30), learning and memory (Logical Memory forms I and II subtests of the Wechsler Memory Scale; ranges, 0-28 and 0-14), and processing speed (Digit Symbol Coding Test of the Wechsler Adult Intelligence Scale; range, 0-135) (eTable 1 in Supplement 2).[18-20] For white participants scoring lower than 19 (with <12 years of education) or lower than 21 (with ≥12 years of education) on the MoCA, nonwhite participants scoring lower than 17 (with <12 years of education) or lower than 19 (with ≥12 years of education) on the MoCA, or any participant with a decrease of 5 or more points from a previous MoCA assessment, a preidentified proxy was administered the Functional Activities Questionnaire, a 10-item measure of functional abilities (range, 0-30).[21]

Participants scoring either higher than 0 on the Functional Activities Questionnaire or scoring 1 or lower on the 5-point Delayed Recall subtest of the MoCA underwent further testing using an extended cognitive battery that measured attention/concentration, verbal and nonverbal memory, language, and executive functions (eTable 1). A validated telephone battery was administered to participants who could not be assessed in person during follow-up.[22] For participants receiving the telephone battery, the Functional Activities Questionnaire was administered if the participant scored below a preset cut point (≤31) on the Modified Telephone Interview for Cognitive Status.[23] If a participant had died or was otherwise

Figure 1. Participant Flow in the Systolic Blood Pressure Intervention Trial (SPRINT)



SBP indicates systolic blood pressure.

unable to communicate by telephone, the Dementia Questionnaire was administered to a prespecified contact.[24] For all tests and questionnaires, validated Spanish translations were used when available. Otherwise, instruments were translated and then back-translated.

In addition to cognitive test scores and proxy functional status reports, all participants were administered a standardized measure of depressive symptoms, perceived health status, and quality of life[25] and reported current medications, medical problems, and current health habits (smoking, alcohol use, and physical activity). Hospitalizations were also recorded as part of a standardized protocol for ascertainment of serious adverse events and all references to treatment group were redacted.[13] These data were reviewed by an expert adjudication panel that included a neurologist, neuropsychologists, geriatricians, and geropsychologists to adjudicate cognitive status. The adjudicators were masked to treatment assignment. Participants were classified into 1 of 3 primary categories: no cognitive impairment, MCI, or probable dementia. Unclassifiable cases were placed in a "cannot classify" category. Each case was reviewed independently by 2 adjudicators using standardized diagnostic criteria for probable dementia and MCI.[26,27] Agreements by the 2 adjudicators were final. Disagreements were discussed by the full panel on regularly scheduled conference calls, with the classification decision achieved by a majority vote of the panel members. No subclassification of probable dementia was made. Additional details of the adjudication process can be found in the trial protocol (Supplement 1).

Duration of Follow-up

The design of the trial included planned cognitive assessments at baseline and at 2 and 4 years of follow-up, as well as at study closeout if it was more than 1 year removed from the 4-year follow-up visit (eFigure 1 in Supplement 2). On August 20, 2015, the Director of the National Heart, Lung, and Blood Institute accepted the data and safety monitoring board's recommendation to inform the investigators and participants of the cardiovascular results after analyses of the primary outcome (composite of cardiovascular events) showed that the monitoring boundary was exceeded at 2 consecutive time points, thus initiating the process to end the BP intervention. Many of the planned year 4 cognitive assessments had not been completed as of this date and so were completed at study closeout while the trial was still providing medication at no cost to participants. However, after the trial was stopped and during the closeout visits, BP management decisions were returned to participants' primary care physicians. After the closeout visit, participants were transitioned to having their BP and medications managed by their primary care physicians and medications were no longer provided by the trial. A final extended follow-up visit, which included cognitive assessment, was conducted between October 2017 and July 2018. For this analysis, the final date of follow-up was July 22, 2018. Adverse events during the intervention phase of the trial have been published previously[13,14,28]; additional adverse event data were not collected during the extended follow-up visits.

Cognitive Outcomes

The primary cognitive outcome was occurrence of probable dementia. Secondary cognitive outcomes included occurrence of MCI and a composite outcome of occurrence of probable dementia or MCI. Mild cognitive impairment was defined as 2 or more consecutive occurrences of an adjudicated classification of MCI (eFigure 2 in Supplement 2). The protocol also specified secondary outcomes examining cognitive decline in the specific cognitive domains of memory and processing speed

Table 1. Baseline Characteristics of Randomized Participants

Characteristics	Treatment Group	
	Intensive (n = 4678)	Standard (n = 4683)
Age, mean (SD), y	67.9 (9.4)	67.9 (9.5)
Aged ≥75 y, No. (%)	1317 (28.2)	1319 (28.2)
Sex, No. (%)		
Male	2994 (64.0)	3035 (64.8)
Female	1684 (36.0)	1648 (35.2)
Race/ethnicity, No. (%)		
White	2698 (57.7)	2701 (57.7)
Black	1379 (29.5)	1423 (30.4)
Hispanic[a]	503 (10.8)	481 (10.3)
Other[b]	98 (2.1)	78 (1.7)
Black race, No. (%)[c]	1454 (31.1)	1493 (31.9)
Systolic blood pressure, mean (SD), mm Hg	139.7 (15.8)	139.7 (15.4)
Tertile, No. (%)[d]		
≤132	1583 (33.8)	1553 (33.2)
>132 to ≤145	1579 (33.8)	1666 (35.6)
>145	1516 (32.4)	1464 (31.3)
Diastolic blood pressure, mean (SD), mm Hg	78.2 (11.9)	78.0 (12.0)
Orthostatic hypotension, No. (%)	345 (7.4)	340 (7.3)
History of cardiovascular disease, No. (%)	940 (20.1)	937 (20.0)
Estimated glomerular filtration rate, mean (SD), mL/min/1.73 m^{2e}	71.8 (20.7)	71.7 (20.6)
<60, No. (%)	1329 (28.5)	1316 (28.3)
Montreal Cognitive Assessment, median (IQR)[f]	23.0 (20.0-26.0)	23.0 (20.0-26.0)
Logical Memory form II, median (IQR)[g]	8.0 (6.0-11.0)	8.0 (6.0-11.0)
Digit Symbol Coding Test, median (IQR)[h]	51.0 (41.0-60.0)	51.0 (41.0-61.0)

Abbreviation: IQR, interquartile range.

[a] Hispanic race/ethnicity encompasses a self-report of being of Spanish, Hispanic, or Latino origin, independent of any other race/ethnicity designation.

[b] Other race/ethnicity includes categories of Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, or other.

[c] Black race includes Hispanic black and black as part of a multiracial identification.

[d] Systolic blood pressure tertiles were based on blood pressure measured at the randomization visit.

[e] Based on the Modification of Diet in Renal Disease Study equation.

[f] Scores range from 0 to 30, with higher scores denoting better cognitive function.

[g] Subtest of the Wechsler Memory Scale. Scores range from 0 to 14, with higher scores denoting better cognitive function.

[h] Subtest of the Wechsler Adult Intelligence Scale. Scores range from 0 to 135, with higher scores denoting better cognitive function.

in a subgroup of participants with complete cognitive testing, the results of which are not presented herein.

Post Hoc Cognitive Outcomes

We also considered sensitivity analyses that relaxed the outcome definition for MCI by examining the time to first occurrence of an adjudication of MCI.

Subgroups

Prespecified subgroups included age (<75 vs ≥75 years), sex, race (black vs nonblack), baseline SBP tertiles (≤132, >132 to <145, and ≥145 mm Hg), and presence of CVD, chronic kidney disease, and orthostatic hypotension at baseline. The trial protocol also specified a subgroup analysis based on the presence of MCI at baseline. All participants were administered the cognitive screening battery at baseline. However, we did not collect additional testing sufficient to adjudicate cognitive status; therefore, this subgroup analysis was not performed.

Statistical Analysis

The primary hypothesis for the cognitive assessments was that the incidence of all-cause probable dementia would be lower for participants assigned to intensive treatment compared with their counterparts assigned to standard treatment over an average of 60 months of follow-up. Although the cognitive outcomes were not used to determine sample size or as part of the sequential monitoring, we estimated that the trial would have an annual incidence rate of 3.1% for dementia in the standard treatment group, with 96% power to detect a 20% reduction (Supplement 1) and 79% power for a 15% reduction.

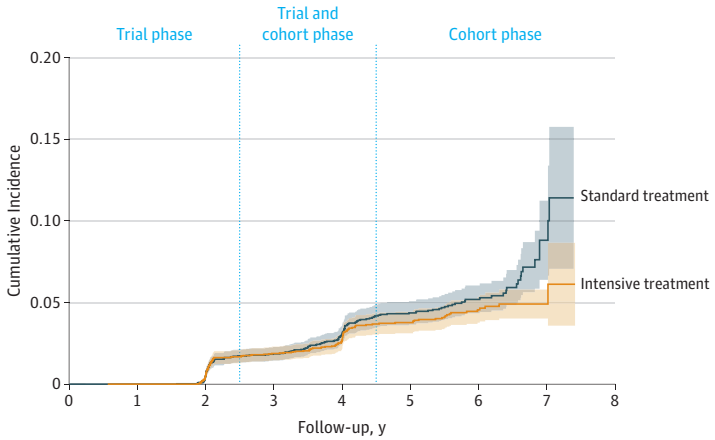
The time to occurrence of probable dementia, MCI, or the composite outcome was compared between the 2 treatment groups using Cox proportional hazards regression, with the baseline hazard function stratified by clinical site. We evaluated the suitability of the proportional hazards assumption using graphical techniques and hypothesis tests based on Schoenfeld residuals.[29] Interactions between treatment effect and prespecified subgroups were assessed with a likelihood ratio test. We conducted sensitivity analyses accounting for the competing risk of death. For participants who died between the study closeout visit and the extended follow-up visit, we did not have consent to contact a proxy to ascertain the exact date of death. Because of this, we used a subdistribution hazard model that allows for interval censoring.[30] We also performed sensitivity analyses to assess the influence of missing data using multiple imputation (eAppendix in Supplement 2). All hypothesis tests were 2-sided and performed at the α=.05 level of significance. There was no adjustment of the significance threshold for the secondary or other end points; because of the potential for type I error, the findings from these analyses should be considered exploratory. All analyses were performed using SAS version 9.4 (SAS Institute Inc) and the R statistical computing environment (http://www.r-project.org).

Results

Study Participants

A total of 9361 participants were randomized between November 2010 and March 2013 (**Figure 1**). Overall, the mean age was 67.9 years (SD, 9.4 years), with 28.2% of participants aged 75 years or older (**Table 1**). Randomized participants were 35.6% female, 30.0% black, and 10.5% Hispanic. The mean SBP at baseline was 139.7 mm Hg (SD, 15.6 mm Hg), and the median MoCA score was 23 (interquartile range, 20-26).

Figure 2. Probable Dementia by Treatment Group



No. at risk

Standard treatment	4285	4282	4168	3886	2829	2107	989	87	0
Intensive treatment	4278	4277	4171	3917	2893	2189	1027	93	0

Shaded regions indicate 95% confidence intervals. Median follow-up time was 5.14 years (interquartile range, 3.91-6.00) for the intensive treatment group and 5.07 years (interquartile range, 3.87-5.98) for the standard treatment group. For group comparison of incidence, hazard ratio, 0.83; 95% CI, 0.67-1.04; *P*=.10.

Blood Pressure

Up until the decision to stop the trial intervention (August 20, 2015), there was a sustained between-group difference in SBP (eFigure 3 in Supplement 2). The mean SBP was 121.6 mm Hg (95% CI, 120.8-122.3 mm Hg) in the intensive treatment group and 134.8 mm Hg (95% CI, 134.1-135.6 mm Hg) in the standard treatment group, resulting in a mean between-group difference of 13.3 mm Hg (95% CI, 12.3-14.3 mm Hg). During the study closeout period (from August 20, 2015, to July 1, 2016), the between-group difference was reduced to 10.5 mm Hg (95% CI, 9.6-11.5 mm Hg), largely attributable to an increase in the mean SBP in the intensive treatment group to 125.0 mm Hg (95% CI, 124.3-125.7 mm Hg) following conclusion of the trial. During the extended follow-up visits, the between-group difference was further reduced to 6.4 mm Hg (95% CI, 4.2-8.5 mm Hg), attributable to a further increase in the mean SBP in the intensive treatment group to 129.2 mm Hg (95% CI, 127.7-130.7 mm Hg).

Follow-up Cognitive Data Collection

In the intensive treatment group, 4278 (91.4%) participants completed at least 1 cognitive assessment during follow-up, compared with 4285 (91.5%) in the standard treatment group (Figure 1). In general, participants who did not complete a cognitive assessment during follow-up were more likely to be female, more likely to be black, had lower cognitive test scores at baseline, and had higher levels of frailty and depressive symptoms compared with participants for whom cognitive status could be ascertained during follow-up (eTable 2 in Supplement 2). Across all follow-up visits, 93.5% of cognitive assessments were conducted in person (eFigure 4 in Supplement 2). With removal of participants who either were deceased, withdrew consent, or were previously adjudicated as having probable dementia, completion rates for cognitive testing were greater than 90% for both treatment groups at the year 2 and year 4 follow-up visits. Completion rates decreased at the extended follow-up visits (61.0% and 59.2%, respectively, for the intensive and standard treatment groups) but were not statistically different by treatment group (*P* = .10). Occurrence of indeterminate adjudications (ie, decisions of "cannot classify") was low and was also similar between the treatment groups (eTable 3 in Supplement 2).

Primary Cognitive Outcome

In the intensive treatment group, 149 participants (7.2 per 1000 person-years) were adjudicated with probable dementia compared with 176 participants (8.6 per 1000 person-years) in the standard treatment group (hazard ratio [HR], 0.83; 95% CI, 0.67-1.04) (**Figure 2** and **Table 2**). The proportional hazards assumption was not severely violated, although there was some indication of an increasing difference between the treatment groups during the later observational phase of follow-up (Schoenfeld *P* = .06). If assessments from the extended follow-up visits were excluded (eTable 4 in Supplement 2), 129 and 140 cases of probable dementia occurred in the intensive and standard treatment groups, respectively (HR, 0.93; 95% CI, 0.73-1.18). There were no significant interactions between treatment group and any prespecified subgroup (**Figure 3**). When death was treated as a competing risk (eFigure 5 in Supplement 2), the results with respect to the effect of intensive treatment on probable dementia were similar (HR, 0.84; 95% CI, 0.68-1.05). Results based on multiple imputation indicated that the incidence of probable dementia was likely underestimated in both treatment groups because of incomplete ascertainment; however, HR estimates were generally unchanged (eTable 5 in Supplement 2).

Secondary Cognitive Outcomes

Mild cognitive impairment occurred in 287 participants in the intensive treatment group and 353 participants in the standard treatment group (14.6 vs 18.3 per 1000 person-years; HR, 0.81; 95% CI, 0.69-0.95). The inference for adjudicated MCI was not changed when the analysis was limited to follow-up through the closeout visits (eTable 4 in Supplement 2). Relaxing

Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

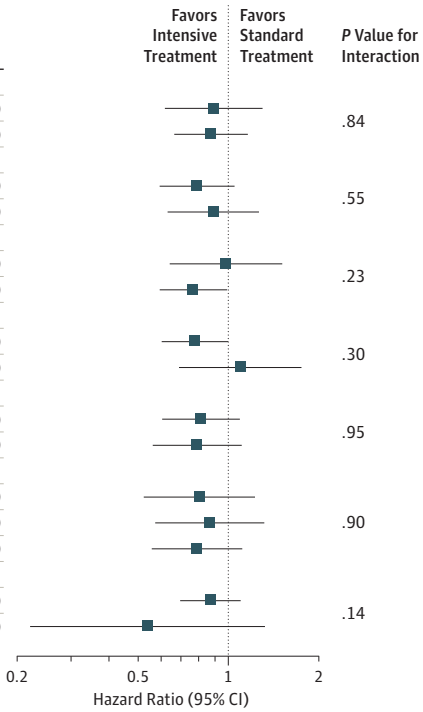
Outcomes	Treatment Group				Hazard Ratio (95% CI)[a]	*P* Value
	Intensive		Standard			
	No. With Outcome/Person-Years	Cases per 1000 Person-Years	No. With Outcome/Person-Years	Cases per 1000 Person-Years		
Probable dementia	149/20 569	7.2	176/20 378	8.6	0.83 (0.67-1.04)	.10
Mild cognitive impairment[b]	287/19 690	14.6	353/19 281	18.3	0.81 (0.69-0.95)	.007
Composite of mild cognitive impairment or probable dementia	402/19 873	20.2	469/19 488	24.1	0.85 (0.74-0.97)	.01

[a] Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

[b] Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.

Figure 3. Probable Dementia in Intensive vs Standard Treatment Groups by Subgroup

	Intensive Treatment		Standard Treatment			
	No. With Probable Dementia	No. of Cases per 1000 Person-Years	No. With Probable Dementia	No. of Cases per 1000 Person-Years	Hazard Ratio (95% CI)	*P* Value for Interaction
Age, y						
<75	54	3.5	60	4.0	0.90 (0.62-1.30)	.84
≥75	95	17.8	116	22.0	0.88 (0.66-1.16)	
Sex						
Male	87	6.6	108	8.2	0.79 (0.59-1.05)	.55
Female	62	8.5	68	9.5	0.89 (0.63-1.27)	
Race						
Black	44	7.2	42	6.7	0.98 (0.64-1.51)	.23
Nonblack	105	7.3	134	9.5	0.77 (0.59-0.99)	
History of cardiovascular disease						
No	109	6.6	138	8.4	0.78 (0.60-1.00)	.30
Yes	40	10.1	38	9.8	1.10 (0.69-1.75)	
Chronic kidney disease						
No	81	5.4	100	6.7	0.81 (0.61-1.09)	.95
Yes	68	12.0	76	14.1	0.79 (0.56-1.11)	
Systolic blood pressure tertile, mm Hg						
≤132	44	6.2	49	7.2	0.80 (0.53-1.23)	.90
>132 to <145	45	6.7	50	7.3	0.87 (0.57-1.32)	
≥145	60	8.8	77	11.5	0.79 (0.56-1.12)	
Orthostatic hypotension						
No	138	7.2	156	8.2	0.87 (0.69-1.10)	.14
Yes	11	7.3	20	13.9	0.54 (0.22-1.33)	



Chronic kidney disease was defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease Study equation. Systolic blood pressure tertiles were based on blood pressure measured at the randomization visit.

the protocol definition of MCI by examining the time to first adjudication of MCI also indicated a significant reduction in favor of the intensive treatment group (44.9 vs 49.8 per 1000 person-years; HR, 0.90; 95% CI, 0.82-0.98) (eTable 5 in Supplement 2). This difference was not significant in the multiple imputation analyses for time to first MCI (eTable 5), as the HR estimates were somewhat attenuated (ranging from 0.92 to 0.94 depending on the parameters of the imputation procedure). There was a significant difference in the composite outcome of MCI or probable dementia favoring the intensive treatment group (20.2 vs 24.1 per 1000 person-years; HR, 0.85; 95% CI, 0.74-0.97). There was a nominally significant interaction between treatment group and presence of chronic kidney disease at baseline with respect to MCI ($P = .04$) (eFigure 6 in Supplement 2); however, this result would not be significant after applying any correction for multiple testing. In addition, there were no significant interactions between treatment assignment and prespecified subgroups with respect to the composite of MCI and probable dementia (eFigure 7 in Supplement 2).

Discussion

This trial showed that intensive BP control to a target of less than 120 mm Hg compared with a target of less than 140 mm Hg did not significantly reduce the incidence of probable dementia. These findings provide important information about intensive BP control, which has previously shown significant benefit for cardiovascular morbidity and mortality.[13,14]

There has been controversy about the benefits and risks associated with lowering SBP levels to below 150 mm Hg.[31-34] One risk that is often cited is the possibility of hypotension and cerebral hypoperfusion resulting in negative effects on the brain.[35] This trial demonstrates no such negative effect; specifically, these results importantly show that intensive BP control did not result in harm to cognition after a median intervention period of 3.34 years and an overall median follow-up of 5.11 years. Moreover, there is some indication that intensive BP control may be beneficial. This is the first trial, to our knowledge, to demonstrate an intervention that significantly reduces the occurrence of MCI, a well-established risk factor for dementia,[36] as well as the combined occurrence of MCI or dementia. However, some caution should be exercised in interpreting this result, both because MCI was not the primary cognitive outcome of the trial and because it is not clear what this effect may mean for the longer-term incidence of dementia. Although MCI considerably increases the risk of progression to dementia, such progression is not certain and reversion to normal cognition is also possible.[36]

Observational studies have suggested that lowering SBP may reduce the risk of cognitive impairment, although the evidence is stronger for BP lowering in middle age compared with later in life.[5,9] Randomized clinical trials such as the Systolic Hypertension in Europe (Syst-Eur) trial[37] and the Hypertension in the Very Elderly Trial (HYVET)[38] suggested a benefit of lowered BP, although the SBP targets evaluated in Syst-Eur and HYVET were much higher than those evaluated in the current trial. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial assessed the effect of similar SBP targets as this trial in patients with type 2 diabetes and found no significant differences in tests of cognitive function. However, ACCORD included a younger population and was not designed to assess adjudicated MCI or dementia.[39] With such variability in BP targets and cognitive outcome definitions, the effect of intensive BP control on cognitive impairment and dementia in older adults remains somewhat uncertain.[10]

Limitations

This study has several limitations. First, the BP intervention was terminated early because of cardiovascular benefit, resulting in both an attenuation of the SBP difference between the treatment groups and a probable loss of power to detect an effect on dementia beyond that point. Second, the trial did not enroll persons with type 2 diabetes, previous stroke, advanced kidney disease, or symptomatic heart failure. Third, the specific choice of thresholds for the MoCA and the Modified Telephone Interview for Cognitive Status to trigger additional testing and adjudication may have underestimated the frequency of MCI. However, there is no indication that such an underascertainment was differential by treatment group. Fourth, loss to follow-up with the extended follow-up visits, though similar for each treatment group, could have also led to underascertainment of outcomes. Fifth, while prevalent dementia was an exclusion criterion, the trial did not adjudicate baseline cognitive status; therefore, we cannot exclude or examine the influence of prevalent MCI at the time of randomization. Sixth, the trial was designed to test 2 different treatment goals and not specific medications; therefore, there is limited ability to discern the relative effect of specific antihypertensive medications on MCI or dementia.

Conclusions

Among ambulatory adults with hypertension, treating to an SBP goal of less than 120 mm Hg compared with a goal of less than 140 mm Hg did not result in a significant reduction in the risk of probable dementia. Because of early study termination and fewer than expected cases of dementia, the study may have been underpowered for this end point.

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SPRINT MIND Authors/Investigators: Jeff D. Williamson, MD, MHS; Nicholas M. Pajewski, PhD; Alexander P. Auchus, MD; R. Nick Bryan, MD, PhD; Gordon Chelune, PhD; Alfred K. Cheung, MD; Maryjo L. Cleveland, MD; Laura H. Coker, PhD; Michael G. Crowe, PhD; William C. Cushman, MD; Jeffrey A. Cutler, MD, MPH; Christos Davatzikos, PhD; Lisa Desiderio, RT; Guray Erus, PhD; Larry J. Fine, MD; Sarah A. Gaussoin, MS; Darrin Harris; Meng-Kang Hsieh, MS; Karen C. Johnson, MD, MPH; Paul L. Kimmel, MD; Manjula Kurella Tamura, MD, MPH; Lenore J. Launer, PhD; Alan J. Lerner, MD; Cora E. Lewis, MD, MSPH; Jennifer Martindale-Adams, EdD, MS; Claudia S. Moy, PhD; Ilya M. Nasrallah, MD, PhD; Linda O. Nichols, PhD, MA; Suzanne Oparil, MD; Paula K. Ogrocki, PhD; Mahboob Rahman, MD; Stephen R. Rapp, PhD; David M. Reboussin, PhD; Michael V. Rocco, MD, MSCE; Bonnie C. Sachs, PhD; Kaycee M. Sink, MD, MAS; Carolyn H. Still, PhD, RN; Mark A. Supiano, MD; Joni K. Snyder, RN; Virginia G. Wadley, PhD; Jennifer Walker, BS; Daniel E. Weiner, MD, MS; Paul K. Whelton, MD; Valerie M. Wilson, MD; Nancy Woolard; Jackson T. Wright Jr, MD, PhD; Clinton B. Wright, MD, MS.

Affiliations of SPRINT MIND Authors/Investigators: Section of Gerontology and Geriatric Medicine, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina (Williamson, Cleveland, Sink, Walker, Wilson, Woolard); Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, North Carolina (Pajewski, Gaussoin, Harris, Reboussin); Department of Neurology, University of Mississippi Medical Center, Jackson (Auchus); Department of Radiology, University of Pennsylvania, Philadelphia (Bryan, Davatzikos, Desiderio, Erus, Hsieh, Nasrallah); Department of Neurology, University of Utah School of Medicine, Salt Lake City (Chelune); Division of Nephrology and Hypertension, University of Utah School of Medicine, Salt Lake City (Cheung); Department of Social Sciences and Health Policy, Wake Forest School of Medicine, Winston-Salem, North Carolina (Coker); Department of Psychology, University of Alabama at Birmingham (Crowe); Preventive Medicine Section, Veterans Affairs Medical Center, Memphis, Tennessee (Cushman, Nichols); Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, Maryland (Cutler, Snyder); Clinical Applications and Prevention Branch, National Heart, Lung, and Blood Institute, Bethesda, Maryland (Fine); Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis (Johnson, Martindale-Adams); Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Disorders, Bethesda, Maryland (Kimmel); Division of Nephrology, Stanford University School of Medicine; Palo Alto, California (Tamura); Neuroepidemiology Section, Intramural Research Program, National Institute on Aging, Bethesda, Maryland (Launer); Department of Neurology, Case Western Reserve University School of Medicine, Cleveland, Ohio (Lerner, Ogrocki); Department of Epidemiology, University of Alabama at Birmingham (Lewis); National Institute of Neurological Disorders and Stroke, Bethesda, Maryland (Moy, C. B. Wright); Department of Medicine, University of Alabama at Birmingham

(Oparil, Wadley); Department of Medicine, Louis Stokes Cleveland Veterans Affairs Medical Center, Case Western Reserve University, Cleveland, Ohio (Rahman); Department of Psychiatry and Behavioral Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina (Rapp); Section of Nephrology, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina (Rocco); Department of Neurology, Wake Forest School of Medicine, Winston-Salem, North Carolina (Sachs); Frances Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, Ohio (Still); Division of Geriatrics, University of Utah School of Medicine, Salt Lake City (Supiano); Division of Nephrology, Tufts Medical Center, Boston, Massachusetts (Weiner); Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana (Whelton); Division of Nephrology and Hypertension, Department of Medicine, Case Western Reserve University, Cleveland, Ohio (J. T. Wright).

Author Contributions: Dr Pajewski had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Williamson, Pajewski, Chelune, Cheung, Cushman, Cutler, Fine, Johnson, Kimmel, Launer, Lerner, Lewis, Moy, Oparil, Rahman, Rapp, Reboussin, Sink, Still, Snyder, Wadley, Walker, Weiner, Whelton, Woolard.
Acquisition, analysis, or interpretation of data: Williamson, Pajewski, Auchus, Bryan, Chelune, Cheung, Cleveland, Coker, Crowe, Cushman, Davatzikos, Desiderio, Erus, Fine, Gaussoin, Johnson, Kimmel, Tamura, Lerner, Martindale-Adams, Nasrallah, Nichols, Oparil, Ogrocki, Rapp, Reboussin, Rocco, Sachs, Sink, Supiano, Wadley, Walker, Weiner, Wilson, Wright.
Drafting of the manuscript: Williamson, Pajewski, Nasrallah, Rapp, Reboussin, Walker, Woolard.
Critical revision of the manuscript for important intellectual content: Williamson, Pajewski, Auchus, Bryan, Chelune, Cheung, Cleveland, Coker, Crowe, Cushman, Cutler, Davatzikos, Desiderio, Erus, Fine, Gaussoin, Johnson, Kimmel, Tamura, Launer, Lerner, Lewis, Martindale-Adams, Moy, Nasrallah, Nichols, Oparil, Ogrocki, Rahman, Rapp, Reboussin, Rocco, Sachs, Sink, Still, Supiano, Snyder, Wadley, Weiner, Whelton, Wilson, Wright.
Statistical analysis: Pajewski, Davatzikos, Gaussoin, Nasrallah, Reboussin, Wilson.
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Supervision: Williamson, Pajewski, Bryan, Coker, Fine, Johnson, Oparil, Rahman, Rapp, Reboussin, Sink, Snyder, Wadley.

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