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Intensive vs Standard Blood Pressure Control in Adults 80 Years or Older: A Secondary Analysis of the Systolic Blood Pressure Intervention Trial

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

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Abstract

OBJECTIVES: To evaluate the effect of intensive systolic blood pressure (SBP) control in older adults with hypertension, considering cognitive and physical function.

DESIGN: Secondary analysis.

SETTING: Systolic Blood Pressure Intervention Trial (SPRINT) PARTICIPANTS: Adults 80 years or older.

INTERVENTION: Participants with hypertension but without diabetes (N = 1167) were randomized to an SBP target below 120 mm Hg (intensive treatment) vs a target below 140 mm Hg (standard treatment).

MEASUREMENTS: We measured the incidence of cardiovascular disease (CVD), mortality, changes in renal function, mild cognitive impairment (MCI), probable dementia, and serious adverse events. Gait speed was assessed via a 4-m walk test, and the Montreal Cognitive Assessment (MoCA) was used to quantify baseline cognitive function.

RESULTS: Intensive treatment led to significant reductions in cardiovascular events (hazard ratio [HR] = .66; 95% confidence interval [CI] = .49–.90), mortality (HR = .67; 95% CI = .48–.93), and MCI (HR = .70; 95% CI = .51–.96). There was a significant interaction ($P < .001$) whereby participants with higher baseline scores on the MoCA derived strong benefit from intensive treatment for a composite of CVD and mortality (HR = .40; 95% CI = .28–.57), with no appreciable benefit in participants with lower scores on the MoCA (HR = 1.33 = 95% CI = .87–2.03). There was no evidence of heterogeneity of treatment effects with respect to gait speed. Rates of acute kidney injury and declines of at least 30% in estimated glomerular filtration rate were increased in the intensive treatment group with no between group differences in the rate of injurious falls.

CONCLUSION: In adults aged 80 years or older, intensive SBP control lowers the risk of major cardiovascular events, MCI, and death, with increased risk of changes to kidney function. The cardiovascular and mortality benefits of intensive SBP control may not extend to older adults with lower baseline cognitive function.

TRIAL REGISTRATION: Clinicaltrials.gov identifier: .

Keywords

cardiovascular disease; hypertension; older adults; cognitive function

The number of adults aged 80 years and older is steadily increasing and expected to reach 7.7% of the population in the United States by 2050.[1] Given that the lifetime risk of developing hypertension is at least 70% by age 80 for whites and blacks in the United States, [2] this demographic shift will induce a growing impact of hypertension and its adverse consequences in older adults. The 2017 American College of Cardiology/American Heart Association blood pressure guidelines recommended treatment to a systolic blood pressure (SBP) below 130 mm Hg in noninstitutionalized ambulatory community-dwelling adults 65 years of age or older.[3] However, hypertension treatment for adults 80 years or older is frequently complicated by multiple chronic conditions such as frailty, polypharmacy, and cognitive impairment.[4,5] Observational analyses indicate an attenuation of the association between elevated blood pressure (BP) and the incidence of vascular and non-vascular disease with increasing age,[6,7] suggesting that the balance of risk to benefit for hypertension treatment may be different for adults 80 years of age or older as compared with adults in their 60s and 70s. Several studies also suggest that older adults with robust functional status may be more likely to benefit from hypertensive therapy, with weaker or null associations between elevated SBP and adverse outcomes in adults with impaired function.[8–10]

Much of the evidence for the benefit of antihypertensive drug therapy in adults 80 years of age or older comes from the Hypertension in the Very Elderly Trial (HYVET) which identified a significant and clinically important reduction in stroke and mortality with the long-acting diuretic indapamide (alone or combined with perindopril) compared with placebo.[11] However, the baseline SBP in HYVET was 160 mm Hg or higher, with participants assigned to indapamide achieving a mean (seated) SBP of 143.5 mm Hg after 2 years of treatment. Thus HYVET provides limited information concerning more intensive treatment of SBP to levels below 140 mm Hg. The Systolic Blood Pressure Intervention Trial (SPRINT) compared treatment to an SBP goal below 120 mm Hg (intensive treatment) with treatment to a goal of below 140 mm Hg (standard treatment) in older adults with hypertension.[12] SPRINT included a large number of participants 75 years or older, with results in this subgroup largely indicating beneficial effects on cardiovascular morbidity and mortality.[13] However, most participants in this age group(55.7%) were between 75 and 80 years of age, and very little was reported specifically for the oldest participants in SPRINT. [14] Here we comprehensively examine a range of outcomes including cardiovascular morbidity and mortality, renal function, adjudicated mild cognitive impairment (MCI) and probable dementia, health-related quality of life (HRQOL), and serious adverse events. We also explore whether baseline impairments in cognitive or physical function modify the effect of intensive BP control on outcomes.

METHODS

The trial design, methods, protocol, and primary results were published previously.[12,13,15] Briefly, SPRINT was a multicenter randomized clinical trial comparing two thresholds for

managing SBP in older adults with hypertension who were at increased risk of cardiovascular disease (CVD). All participants 80 years or older were considered at increased risk for CVD by virtue of their age. Exclusion criteria included residence in a nursing home, diagnosis of dementia or use of medications for dementia therapy, prevalent diabetes, or a history of stroke. Participants were randomized to either an SBP goal of below 120 mm Hg (intensive treatment) or below 140 mm Hg (standard treatment), with the randomization stratified by clinic site. The study was approved by an institutional review board at each participating site, and each participant provided written informed consent.

Outcomes

Two separate committees, unaware of treatment assignment and using formal criteria and operations manuals, adjudicated protocol-specified clinical outcomes related to (1) CVD morbidity and mortality, and (2) MCI and probable dementia. The primary CVD outcome was a composite of nonfatal myocardial infarction, acute coronary syndrome not resulting in a myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular causes. Secondary outcomes included all-cause mortality and the composite of the primary CVD outcome and all-cause mortality. Ascertainment of cognitive outcomes was previously described.[16] Cognitive outcomes included the occurrence of probable dementia, MCI, and a composite outcome of probable dementia or MCI.

Serious Adverse Events

Serious adverse events (SAEs) were defined as events that were fatal or life threatening, resulted in significant or persistent disability, required hospitalization or resulted in prolonged hospitalization, or medical events that the investigator judged to be a significant hazard or harm to the participant and required medical or surgical intervention to prevent harm. The following conditions of interest were reported as adverse events if they were evaluated in an emergency department: hypotension, syncope, injurious falls, electrolyte abnormalities, and bradycardia. Episodes of acute kidney injury (or acute renal failure) were monitored if they led to hospitalization and were reported in the hospital discharge summary.

Duration of Follow-Up

Recruitment for the overall trial began on November 8, 2010. The director of the National Heart, Lung, and Blood Institute accepted the Data Safety and Monitoring Board recommendation to stop the intervention on August 20, 2015. Clinical outcomes in this report (with the exception of cognition) are based on additional follow-up including study “closeout” visits through July 1, 2016. During this time frame, the trial was still providing medication at no cost to participants; however, BP management decisions were gradually returned to participants’ primary care physicians. For cognitive outcomes, follow-up also included an extended follow-up visit, conducted between October 2017 and July 2018.

Study Measurements

Sociodemographic data were collected at baseline, with race or ethnicity information collected via self-report. Body mass index was calculated as weight in kilograms divided by height in meters squared. The estimated glomerular filtration rate (eGFR) was calculated by

the four-variable Modification of Diet in Renal Disease study equation.[17] Comorbidity was defined based on the index of Selim et al.[18] BP at all study visits was determined using the mean of three properly sized automated cuff readings, taken 1 minute apart after 5 minutes of quiet rest.[19]

Gait speed was measured at baseline via a timed 4-m walk, performed twice at the participant's usual pace from a standing start.[20] The use of a walking assistive device was permitted if typically used by the participant to walk short distances. The faster of the two gait speeds in meters per second was used in this analysis. Gait speeds slower than .20 m/s and faster than 2.0 m/s were set to missing.

Patient-reported outcomes assessed annually included the Veterans RAND 12-Item Health Survey (VR-12) that describes physical and mental HRQOL.[21] Scores on the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the VR-12 are standardized with a mean of 50 and a standard deviation (SD) of 10; scores range from 0 to 100, with higher scores denoting better physical health and mental health, respectively.

Exploratory Analyses of Cognitive and Physical Function

We examined the effect of decrements in cognitive or physical function based on gait speed and scores on the Montreal Cognitive Assessment (MoCA).[22] Participants were categorized as having lower physical function if their gait speed was slower than .8 m/s.[23] Lower cognitive function was defined as scoring 18 or lower (less than high school education) or 20 or lower (high school education or higher) on the MoCA. This roughly corresponds to the estimated normative 25th percentile at 80 years of age in the Irish Longitudinal Study of Aging.[24]

Statistical Analysis

All analyses were based on intention to treat. The time to occurrence of the primary cardiovascular outcome, MCI, probable dementia, and incident SAEs was compared using the subdistribution hazard model of Fine and Gray accounting for the competing risk of death (noncardiovascular death for the primary CVD outcome).[25] All-cause mortality and composite outcomes including all-cause mortality were compared between treatment groups using Cox proportional hazards regression. For both modeling approaches, the baseline hazard function was stratified by clinical site.[26] We used linear mixed-effect models to compare longitudinal trajectories for BP and HRQOL between the treatment groups. The models included random effects for participants and clinic site to account for longitudinal assessments and correlations between participants at the same clinic site. For the HRQOL measures, effect estimates are expressed as an annual slope, assuming linear change over time at the group level. We included time by randomization group interaction terms to test whether the changes in each of the longitudinal outcomes differed between the treatment groups. All hypothesis tests were meant to be hypothesis generating and conducted at an α level of .05. Because we report 40 hypothesis tests (considering multiple subgroups and a range of outcomes), there is an 87% chance that at least one test would be significant at the .05 level assuming independence between tests. All analyses were performed using SAS software v.9.4 and the R Statistical Computing Environment.

RESULTS

Baseline characteristics of the 1167 randomized participants 80 years or older are shown in Table 1. The mean age was 83.5 ±3.2 years (SD), with 3.3% participants older than 90 years at baseline. Most of the participants were male (61.2%), white (76.0%), with a mean systolic BP of 142.6 ± 16.1 mm Hg. Most (89.8%) had at least three comorbid conditions, 54.7% were taking at least five medications, and 27.2% had a history of CVD. The mean gait speed was .87 ± .23 m/s, with 409 (36.5%) participants having a gait speed shower than .8 m/s. The median MoCA score was 22, with 413 (35.8%) participants scoring below the education-specific normative 25th percentiles.

Blood Pressure and Medication Use during Follow-Up

SBP over the course of follow-up is shown in Figure 1. During the intervention phase of the trial, mean SBP averaged 123.9 mm Hg and 135.3 mm Hg in the intensive and standard treatment groups, respectively, for a mean difference of 11.5 mm Hg (95% confidence interval [CI] = 10.6 – 12.4 mm Hg; Supplementary Table S1). Among those in the intensive treatment group, the proportion taking three or more classes of antihypertensive medications was 29.5% at baseline and increased to 48.6% at the 1-year follow-up. Conversely, the proportion taking three or more classes decreased in the standard treatment group, moving from31.4% to 25.0%. During the extended follow-up visits, the between-group difference in SBP was attenuated to 5.6 mm Hg (95% CI = 2.7–8.6 mm Hg), primarily due to an increase in the mean SBP to 130.7 mm Hg in the intensive treatment group. The between-group difference in mean SBP did not appreciably differ by MoCA score or gait speed (Supplementary Table S1).

Although a robust between-group SBP difference was achieved, participants in the intensive treatment group tended not to have SBPs consistently below the target of 120 mm Hg. From the 6-month study visit to the end of the interventional phase of the trial, 303 (54.7%) participants in the intensive treatment group achieved at least 50% of their SBP readings below 120 mm Hg, with 96 (17.3%) participants achieving at least 80% of their SBP readings below 120 mm Hg (Supplementary Table S2). Participants in the intensive treatment group were more consistently controlled below 130 mm Hg; 437 (78.9%) and 252 (45.9%) achieved 50% and 80% of their SBP readings below 130 mm Hg, respectively.

Clinical Outcomes

In the intensive treatment group, 75 participants experienced a primary composite CVD event compared with 106 participants in the standard treatment group (hazard ratio [HR] = .67; 95% CI = .50–.90) (Table 2). Participants in the intensive treatment group also experienced a reduction in all-cause mortality (HR = .67; 95% CI = .49–.92). For both incident CVD events and mortality, significant interactions were found between subgroups based on MoCA score and treatment group. For example, a strongly beneficial effect of intensive treatment on all-cause mortality was found (HR = .39; 95% CI = .24–.64) for participants with MoCA scores above the normative 25th percentiles. In contrast, the rate of all-cause mortality was numerically higher in participants scoring at or below the normative 25th percentiles randomized to intensive treatment (HR = 1.19; 95% CI = .72–1.97;

interaction P value = .003). There was an increased risk of experiencing a 30% reduction in eGFR (HR = 3.41; 95% CI = 1.92–6.06) with intensive treatment, with the relative effect largely independent of cognitive and physical function. The incidence of probable dementia was similar between the treatment groups; however, participants in the intensive treatment group had a lower risk of MCI (HR = .72; 95% CI = .53–.98; Table 3). No evidence of heterogeneity for the cognitive outcomes by either MoCA score or gait speed was observed.

Serious Adverse Events

In the intensive treatment group, SAEs occurred in 340 participants compared with 353 participants in the standard treatment group (HR = .92; 95% CI = .79–1.07; Table 4). Rates of acute kidney injury or renal failure (HR = 2.12; 95% CI = 1.37–3.26) were increased in the intensive treatment group; however, no difference was observed in the incidence of injurious falls (HR = .93; 95% CI = .64–1.36). There were no significant interactions for SAEs by gait speed (Supplementary Table S3). Participants in the intensive treatment group had a higher rate of laboratory alerts for serum sodium values below 130 mmol/L (HR = 1.78; 95% CI = 1.03–3.05; Supplementary Table S4).

Health-Related Quality of Life

No differences were found between the intensive and standard treatment groups in mental quality of life based on the VR-12 MCS score, either overall or by MoCA score or gait speed (Supplementary Table S5). A smaller rate of decline was observed in the PCS score for participants in the intensive treatment group (mean difference = .33; 95% CI = .06–.60; P = .02). This roughly corresponds to a mean difference of slightly more than 1 point over 4 years, which is generally thought to be a small effect.[27]

DISCUSSION

Participants 80 years or older randomized to an intensive SBP target of below 120 mm Hg as compared with a target of below 140 mm Hg experienced a decreased risk of cardiovascular morbidity and mortality, MCI, and all-cause mortality. These effects were accompanied by an increased risk of declines in renal function and an increased risk of acute kidney injury but not an increased risk of injurious falls. In general, these results point to a favorable risk benefit profile for intensive BP control in adults 80 years or older, given other work from SPRINT indicating that most cases of acute kidney injury were transient, eventually leading to recovery of kidney function.[28] In addition, the lack of increased risk of injurious falls is especially critical given recent statistics indicating an increasing mortality rate due to falls in adults 75 years or older and the concern that hypotension can result in falls.[29]

Analyses of the Systolic Hypertension in the Elderly Program suggested differential effects of hypertension treatment based on the presence or absence of physical activity limitations.[9] Here we did not observe differential treatment effects with respect to gait speed but did find rather striking differences with respect to cognitive function. Participants with higher baseline cognitive function (>60% of participants ≥80 y) derived a strong benefit from intensive SBP control with respect to CVD and mortality, whereas participants with lower cognitive function randomized to intensive SBP control experienced numerically higher

rates of CVD and mortality. Note that a similar pattern of effect also holds with respect to CVD and mortality among the larger set of participants 75 years or older in SPRINT (Supplementary Table S6). This result was somewhat unexpected given previous analyses from HYVET[30] and SPRINT[13] that examined heterogeneity through the use of frailty indices that incorporate measures of cognitive and physical function. Those analyses did not suggest any significant heterogeneity in the intervention effect in either trial by frailty status, despite a clear gradient of risk whereby participants with higher frailty index scores experienced higher rates of CVD and mortality.

Although our results add support to considering cognitive function in clinical decision making for hypertension therapy,[31] the precise threshold at which inaction or even deprescribing should be preferred is unclear.[5] One limitation of SPRINT's design is that the presence of MCI was not adjudicated at baseline, and so we were forced to use an ad hoc categorization of cognitive status based on the MoCA. Although we categorized participants based on age and education-specific normative data, the thresholds we used were derived from an Irish population and have not been validated. Focusing on a general cognitive screening instrument like the MoCA has advantages in terms of clinical implementation, but there are numerous barriers to routine objective measurement of cognitive function. Although the Medicare Annual Wellness Visits provide an appealing context for ascertaining function, they are underused[32] and may not adequately detect impairment with respect to cognition.[33] In addition, there are a number of recent concerns with the MoCA specifically related to monetization.[34]

Moving beyond function, several other aspects of these results should be considered. First, most SPRINT participants 80 years or older had ages that were clustered between 80 and 85 years, with only 24.9% and 3.3% (of those ≥80 y) older than 85 and 90 years of age at the time of randomization. Therefore, the SPRINT results are most informative for adults 85 years of age or younger, and they are less relevant for intensification of antihypertensive therapy in adults older than 85 years. A second consideration is that participants 80 years or older randomized to intensive SBP control averaged a mean SBP of 125 mm Hg during the interventional phase of the trial, with less than 10% consistently controlled to below 120 mm Hg, despite the treatment target of below 120 mm Hg and systematic measurement of BP.[19] It is clear that achieved SBP with more intensive hypertensive therapy will tend to be higher in this age range as compared with younger adults. This difference needs to be considered in light of differences between the automated protocol-based BP measurement procedure used in SPRINT and what is typically done in clinical practice.[35] Finally, given that this is a secondary analysis, our results should be interpreted with caution, also recognizing more general limitations of SPRINT including generalizability of the cohort and early cessation of the trial intervention.[36,37]

In conclusion, in adults aged 80 years or older, intensive SBP control lowers the risk of major cardiovascular events, MCI, and death, with increased risk of changes to kidney function. The cardiovascular and mortality benefits of intensive SBP control may not extend to older adults with lower cognitive function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Sponsor's Role: The SPRINT steering committee designed and conducted the study including the collection and management of the data. Scientists at the National Institutes of Health (NIH; the sponsor) as a group and the principal investigator of the Veterans Affairs clinical network had one vote on the steering committee of the trial that had seven voting members. The NIH and the US Department of Veterans Affairs had roles in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript but not in the decision to submit the manuscript for publication.

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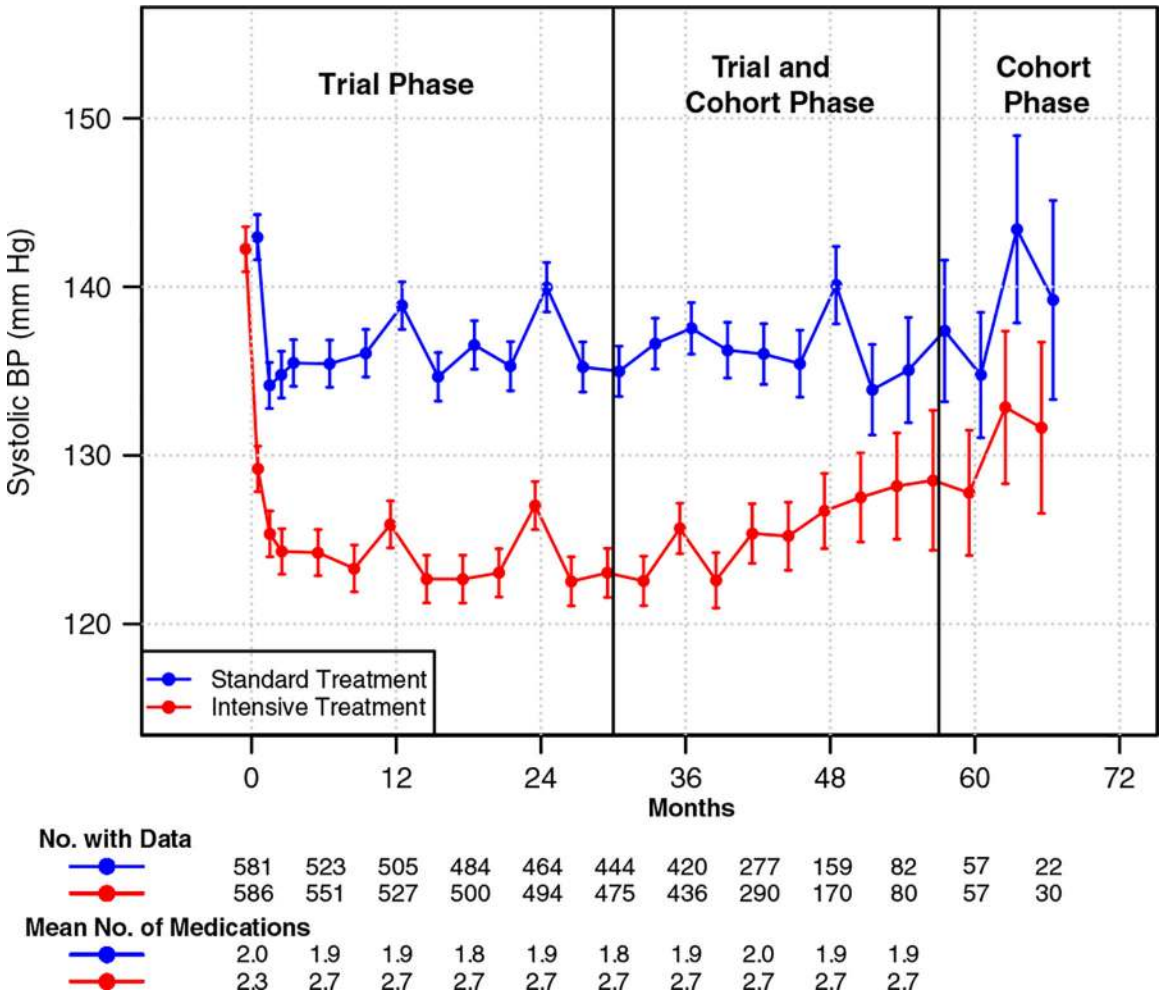

Figure 1.

Systolic blood pressure in the two treatment groups over the course of follow-up. The systolic blood pressure (SBP) target was <120 mm Hg in the Intensive Treatment group, and < 140 mm Hg in the Standard Treatment group. Trial phase includes follow-up through the decision to stop the intervention on August 20, 2015; cohort phase denotes visits that occurred after that date. Points indicate least square means based on linear mixed model with error bars denoting 95% confidence intervals.

Table 1.

Baseline Characteristics of Participants Aged 80 Years or Older

	Intensive treatment N = 586	Standard treatment N = 581
Age		
Mean (SD), y	83.3 (3.0)	83.7 (3.3)
>85 y, n (%)	136 (23.2)	154 (26.5)
>90 y, n (%)	16 (2.7)	22 (3.8)
Female sex, n (%)	221 (37.7)	231 (39.8)
Race/Ethnicity, n (%)		
White	442 (75.4)	445 (76.6)
Black	95 (16.2)	93 (16.0)
Hispanic	42 (7.2)	38 (6.5)
Other	7 (1.2)	5 (.9)
Body mass index, mean (SD), kg/m^2	27.1 (4.8)	27.0 (4.6)
Seated blood pressure, mean (SD), mm Hg		
Systolic	142.2 (15.6)	142.9 (16.6)
Diastolic	70.0 (11.3)	70.0 (11.2)
Orthostatic hypotension, n (%)	55 (9.5)	59 (10.2)
History of CVD, n (%)	165 (28.2)	152 (26.2)
Estimated GFR[a]		
Mean (SD), mL/min/1.73 m^2	60.9 (18.3)	59.6 (17.8)
<60 mL/min/1.73 m^2, n (%)	288 (49.6)	303 (52.5)
Urinary albumin to creatinine ratio, median (IQR), mg/g	15.0 (8.0–39.4)	16.1 (9.0–41.4)
No. of medications, mean (SD)	6.6 (3.6)	6.4 (3.6)
No. of antihypertensive agents, mean (SD)	1.9 (1.0)	1.9 (1.1)
Statin use, n (%)	287 (49.7)	305 (53.1)
Aspirin use, n (%)	364 (62.3)	339 (58.5)
Gait speed		
Median (IQR), m/s	.86 (.72–1.00)	.87 (.73–1.02)
Speed <.8 m/s, n (%)	204 (36.2)	205 (36.8)
MoCA score, n (%)[b]	22 (19–24)	22 (19–24)
≤18 (<HS)/ ≤20 (≥HS)	208 (36.0)	205 (35.5)
VR-12 PCS, mean (SD)[c]	42.4(10.4)	43.4 (9.7)
VR-12 MCS, mean (SD)[c]	54.6 (8.2)	54.9 (8.6)

Abbreviations: CVD, cardiovascular disease; GFR, glomerular filtration rate; HS, high school education; IQR, interquartile range; MCS, Mental Component Summary; MoCA, Montreal Cognitive Assessment; PCS, Physical Component Summary; SD, standard deviation; VR-12, Veterans RAND 12-Item Health Survey.

[a]Based on the four-variable Modification of Diet in Renal Disease equation.

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

[c]Scores on the PCS and MCS of the VR-12 are standardized with a mean of 50 and an SD of 10; scores range from 0 to 100, with higher scores denoting better physical health and mental health, respectively.

Table 2.

Cardiovascular, Mortality, and Renal Outcomes by Treatment Group, Montreal Cognitive Assessment Score, and Gait Speed

	Intensive treatment n/CIF	Standard treatment n/CIF	Hazard ratio (95% Cl)	Interaction *P* value
Primary CVD outcome				
Overall	75/.13	106/.18	.67 (.50-.90)	
MoCA score				.01
>18 (<HS)/>20 (≥HS)	37/.11	72/.19	.49 (.33–.73)	
≤18 (<HS)/ ≤20 (≥HS)	35/.16	34/.16	1.04 (.65–1.66)	
Gait speed				.24
≥8 m/s	38/.09	62/. 18	.56 (.37–.84)	
<.8 m/s	33/.18	41/.19	.79 (.50–1.23)	
All-cause mortality				
Overall	69/.11	92/.15	.67 (.49-.92)	
MoCA score				.003
>18 (<HS)/>20 (≥HS)	24/.06	57/.15	.39 (.24-.64)	
≤18 (<HS)/ ≤20 (≥HS)	42/.21	35/.17	1.19 (.72–1.97)	
Gait speed				.23
≥8 m/s	33/.09	49/.14	.57 (.36–.90)	
<.8 m/s	33/.15	38/.18	.90 (.56–1.47)	
Primary CVD outcome + mortality				
Overall	111/.20	152/.25	.65 (.51–.83)	
MoCA score				<.001
>18 (<HS)/>20 (≥HS)	47/.13	106/.27	.40 (.28–.57)	
≤18 (<HS)/ ≤20 (≥HS)	60/.31	46/.23	1.33 (.87–2.03)	
Gait speed				.13
≥8 m/s	58/.16	91/.26	.55 (.40 .78)	
<.8 m/s	49/.26	55/.26	.79 (.54–1.16)	
30% decline in eGFR				
Overall	48/.09	17/.03	3.41 (1.92–6.06)	
MoCA score				.77
>18 (<HS)/>20 (≥HS)	30/.08	12/.03	2.97 (1.50–5.88)	

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	Intensive treatment n/CIF	Standard treatment n/CIF	Hazard ratio (95% CI)	Interaction *P* value
≤18 (<HS)/ ≤20 (≥HS)	18/.10	5/.03	3.14 (1.21–8.17)	
Gait speed				.98
≥.8 m/s	26/.08	8/.02	3.47 (1.46–8.27)	
<.8 m/s	22/.12	9/.04	3.63 (1.59–8.29)	

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HS, high school education; MoCA, Montreal Cognitive Assessment.

Note: CIF indicates cumulative incidence of event at median length of follow-up for each outcome. Median length of follow-up was 3.61 years for the primary CVD outcome, 3.75 years for all-cause mortality, 3.73 years for the composite of the primary CVD outcome and all-cause mortality, and 3.55 years for a 30% decline in eGFR. Primary CVD outcome includes nonfatal myocardial infarction, acute coronary syndrome not resulting in a myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular causes. Renal outcome reflects ≥30% reduction in eGFR from baseline, measured twice at least 90 days apart. Hazard ratios reflect a comparison of the intensive treatment group vs standard treatment group based on Fine and Gray subdistribution hazard model accounting for the competing risk of death (for outcomes not including all-cause mortality), and Cox proportional hazards regression for outcomes including all-cause mortality.

Table 3.

Cognitive Outcomes by Treatment Group, Montreal Cognitive Assessment Score, and Gait Speed

	Intensive treatment No./CIF	Standard treatment No./CIF	Hazard ratio (95% CI)	Interaction *P* value
Probable dementia				
Overall	63/.12	65/.12	1.06 (.75–1.49)	
MoCA score				.39
>18 (<HS)/>20 (≥HS)	27/.07	22/.05	1.15 (.65–2.05)	
≤18 (<HS)/ ≤20 (≥HS)	35/.23	43/.24	.89 (.55–1.44)	
Gait speed				.25
≥.8 m/s	28/.08	30/.07	.86 (.51–1.45)	
<.8 m/s	34/.22	33/.20	1.33 (.82–2.18)	
MCI				
Overall	73/.15	95/.21	.72 (.53–.98)	
MoCA score				.71
>18 (<HS)/>20 (≥HS)	29/.09	34/.11	.92 (.57–1.51)	
≤18 (<HS)/ ≤20 (≥HS)	44/.29	60/.42	.77 (.51–1.15)	
Gait speed				.45
≥.8 m/s	43/.14	48/.17	.84 (.55–1.29)	
<.8 m/s	27/.19	42/.28	.64 (.38–1.07)	
MCI and probable dementia				
Overall	122/.24	139/.28	.85 (.67–1.09)	
MoCA score				.68
>18 (<HS)/>20 (≥HS)	46/.14	49/.14	.96 (.64–1.45)	
≤18 (<HS)/ ≤20 (≥HS)	75/.44	89/.54	.84 (.60–1.17)	
Gait speed				.91
≥.8 m/s	63/.18	68/.21	.89 (.63–1.27)	
<.8 m/s	55/.35	66/.40	.84 (.58–1.22)	

Abbreviations: CI, confidence interval; HS, high school education; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment.

Note: CIF indicates cumulative incidence of event at median length of follow-up for each outcome. Median length of follow-up was 4.07 years for probable dementia, 4.01 years for MCI, and 4.06 years for the composite of MCI and probable dementia. Hazard ratios reflect a comparison of the intensive treatment group vs standard treatment group based on the Fine and Gray subdistribution hazard model accounting for the competing risk of death.

Table 4.

Serious Adverse Events by Treatment Group and Montreal Cognitive Assessment Score

	Intensive treatment No./CIF	Standard treatment No./CIF	Hazard ratio (95% Cl)	Interaction *P* value
All SAEs				
Overall	340/.60	353/.61	.92 (.79–1.07)	
MoCA score				.04
>18 (<HS)/>20 (≥HS)	207/.58	228/.61	.82 (.68–.99)	
≤18 (<HS)/ ≤20 (≥HS)	129/.63	124/.60	1.14 (.87–1.50)	
Hypotension				
Overall	18/.03	9/.01	2.02 (.91–4.48)	
MoCA score				.24
>18 (<HS)/>20 (≥HS)	12/.03	8/.02	1.54 (.63–3.74)	
≤18 (<HS)/ ≤20 (≥HS)	6/.03	1/<.01	6.09 (.76–48.80)	
Syncope				
Overall	21/.03	19/.02	1.10 (.61–1.96)	
MoCA score				.03
>18 (<HS)/>20 (≥HS)	9/.02	14/.03	.63 (.27–1.49)	
≤18 (<HS)/ ≤20 (≥HS)	12/.06	5/.02	2.56 (.88–7.42)	
Bradycardia				
Overall	26/.05	27/.04	.91 (.54–1.56)	
MoCA score				.20
>18 (<HS)/>20 (≥HS)	15/.04	20/.05	.76 (.38–1.49)	
≤18 (<HS)/ ≤20 (≥HS)	11/.06	7/.04	1.75 (.70–4.38)	
Electrolyte abnormality				
Overall	30/.05	26/.04	1.26 (.76–2.10)	
MoCA score				.35
>18 (<HS)/>20 (≥HS)	19/.05	13/.03	1.64 (.81–3.29)	
≤18 (<HS)/ ≤20 (≥HS)	11/.05	13/.07	1.38 (.61–3.12)	
injurious fall				
Overall	49/.08	53/.09	.93 (.64–1.36)	
MoCA score				.60

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	Intensive treatment No./CIF	Standard treatment No./CIF	Hazard ratio (95% CI)	Interaction *P* value
>18 (<HS)/>20 (≥HS)	31/.08	29/.07	1.07 (.66–1.74)	
≤18 (<HS)/ ≤20 (≥HS)	18/.09	24/. 13	.93 (.48–1.78)	
AKI				
Overall	56/.10	32/.05	2.12 (1.37–3.26)	
MoCA score				.63
>18 (<HS)/>20 (≥HS)	36/.10	17/.04	2.28 (1.29–4.05)	
≤18 (<HS)/ ≤20 (≥HS)	20/.11	15/.08	2.53 (1.20–5.31)	

Abbreviations: AKI, acute kidney injury or renal failure; CI, confidence interval; HS, high school education; MoCA, Montreal Cognitive Assessment; SAE, serious adverse event.

Note: CIF indicates cumulative incidence of event at median length of follow-up for each outcome. Median length of follow-up was 3.76 years for all SAEs, 3.55 years for hypotension, syncope, and bradycardia, 3.56 years for electrolyte abnormalities, and 3.57 years for injurious falls and AKI. An SAE was defined as an event that was fatal or life threatening that resulted in clinically significant or persistent disability, required or prolonged a hospitalization, or was judged by the investigator to represent a clinically significant hazard or harm to the participant that might require medical or surgical intervention to prevent one of the other events listed above. An injurious fall was defined as a fall that resulted in evaluation in an emergency department or in hospitalization. AKI was coded if the diagnosis was listed in the hospital discharge summary and believed by the safety officer to be one of the top three reasons for admission or continued hospitalization.

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