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SPRINT REVISITED. UPDATED RESULTS AND IMPLICATIONS

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Abstract

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The Systolic Blood Pressure Intervention Trial (SPRINT) results have influenced clinical practice but have also generated discussion regarding the validity, generalizability and importance of the findings. Following the SPRINT primary results manuscript in 2015, additional results and analyses of the data have addressed these concerns. The primary objective of this manuscript is to respond to key questions that have been raised.

The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated the effectiveness of treating SBP to levels well below those previously recommended in US and European BP guidelines.[1] The SPRINT results have informed guideline committees in recommending treatment to SBP targets lower than previously advised.[2–4] However, some of the SPRINT findings have generated discussion, and questions have been raised regarding their application in clinical practice. These include generalizability, validity of the outcome measures (especially heart failure), the methods used for event ascertainment, the effect size of the intervention benefit, and safety and tolerability of the <120 mmHg target.[5, 6] Following the SPRINT primary results publication in 2015, additional reports from SPRINT have addressed many of these concerns. This manuscript reviews evidence for validity and potential clinical implications of the SPRINT findings.

Keywords

heart failure; controlled clinical trial; myocardial infarction; hypertension; blood pressure; cardiovascular disease

SPRINT Design Elements

SPRINT recruited 9,361 adults ≥50 years who were at increased risk for cardiovascular disease (CVD) and had an average SBP 130–180 mmHg. They were randomized to a SBP treatment goal of either <120 mmHg (Intensive) or <140 mmHg (Standard) (Table S1).[1, 7–9] In order to maintain SBP separation between randomized groups, the protocol included a provision to taper treatment in the Standard group for SBP <135 on two consecutive visits or any single visit with SBP <130.

The trial was conducted at 102 clinical practice sites in the United States, including Puerto Rico. Clinical outcomes were assessed at specified follow-up visits using a prospective randomized open-blinded end point (PROBE) design and adjudicated by experienced, trained physicians blinded to treatment assignment using a well-documented pre-specified process. A detailed protocol and manual of procedures (MOP) were developed prior to starting the trial.[8] The primary outcome was a CVD composite of myocardial infarction, stroke, acute coronary syndrome (ACS), acute decompensated heart failure (ADHF), and CVD death. Antihypertensive drug treatment regimens were recommended based on best evidence from clinical trials, but the ultimate choice of therapy was made by the physician site investigators.

Generalizability of BP Measurements in SPRINT

Critics have asserted that the SPRINT BP measurement method was different from what was used in previous BP treatment trials and have questioned the generalizability of SPRINT BP values to routine clinical practice.[5] A primary goal of BP measurement in SPRINT was to standardize readings across the trial and to obtain accurate estimates of the BP level.

Procedures for measurement of BP in SPRINT were generally consistent with existing recommendations and similar to those used in other clinical outcome trials.[10] Each clinical site was provided an Omron 907XL automatic oscillometric BP measurement device. Oscillometric BP measurement devices were used in at least 11 hypertension treatment trials prior to SPRINT.[10] Some questioned the validity of BP readings in SPRINT due to reports that they were obtained with staff absent from the room. This was postulated to result in substantially lower BP values than those obtained in other trials or clinical practice.[5, 11–14] However, the SPRINT protocol did not specify whether staff should be present or absent during BP measurement, and the SPRINT MOP recommended but did not require clinic staff to be out of the room during the rest period prior to BP measurement.

Because the details of BP measurements in SPRINT became a focus of attention, clinics were surveyed immediately after completing their study closeout visits to inquire whether site staff were usually in (attended measurements) or out of the room (unattended measurements) during the rest period and/or during BP measurement. Staff presence or absence was not associated with significant differences in levels of BP, major study outcomes, or safety events (Table S2).[15] At least six other reports have concluded that staff attendance, per se, has limited effect on BP estimation with none reporting a SBP difference ≥2 mmHg.[16–18] In a randomized controlled trial that mimicked the procedures used in SPRINT, the average differences in attended compared to unattended SBP and DBP values were 1.5 and 0 mmHg, respectively.[19]

In clinical practice, BP is often measured with little attention to quality control and may overestimate average SBP by as much as 10–15 mmHg compared to values obtained using guideline recommended methods that have been employed in most landmark antihypertensive drug treatment trials.[20] In some patients, however, routine clinic values are lower compared to guideline recommended measurements. There is no accurate means to estimate the “true” level of BP using poor quality measurements. These findings underscore the importance of BP measurement using the methods recommended in guidelines[2, 21] to derive the benefits obtained in clinical trials. However, staff attendance or absence, per se, does not appear to be a major factor in accuracy of BP estimation.

SUMMARY OF SPRINT FINDINGS

Cardiovascular Outcomes

Achieved median and mean BPs overall and in the pre-specified and other subgroups of interest are provided in Table 1 and Table S3. During trial follow-up, the average achieved median SBPs in the Intensive and Standard groups, respectively, were 119.2 and 135.8 mmHg after the 6-month drug titration period. In the 2015 SPRINT main results report, the

primary outcome and all-cause mortality were 25% (p<0.001) and 27% (p=0.003) lower in the Intensive compared to Standard group.[1] This included a 43% reduction (p=0.005) for CV death and 38% reduction (p=0.002) for ADHF. Results from a subsequent publication, with 56 additional adjudicated primary outcome events, are shown in Table 2.[22]

In this analysis, the primary outcome and all-cause mortality were 27% and 25% lower in the Intensive compared to Standard group, respectively. A significant reduction was evident even when ADHF was excluded from the primary outcome.[22] The reduction in primary outcome events in the Intensive group was seen in the pre-specified subgroups defined by categories of age, gender, levels of baseline SBP presence or absence of CVD history or CKD, and Black or non-Black race (Fig 1). In the 2,636 non-institutionalized participants who were aged ≥75 years at baseline, the benefits were similar, resulting in prevention of primary outcome events and all-cause mortality for one in every 28 and 41 Intensive participants, respectively. [9]In post hoc analyses, the findings were similar in Hispanics, frail older adults, and in those with metabolic syndrome or prediabetes (Figs 1,2). Meta-analyses of trials that have compared random assignment to different levels of BP provide similar results, whether or not the SPRINT results are included.[23–26]

Validity of the Heart Failure Findings

The 38% reduction in ADHF in those randomized to Intensive compared to Standard therapy has also been questioned.[27] The diagnosis of ADHF in SPRINT was based on rigorous, objective criteria that required either a hospitalization or emergency department visit which necessitated intravenous therapy (diuretic or inotropic agents) for a clinical syndrome that presented with multiple signs and symptoms consistent with ADHF.[28] In addition, the ADHF designation required adjudication by a committee of experienced clinicians who were blinded to the participant's randomization and followed standardized procedures outlined in the MOP. In multivariable analysis, participants who developed ADHF during the trial had a 27-fold higher risk of CVD death, a 16-fold higher risk of myocardial infarction, and a 10-fold increased risk of death from any cause compared with those who did not develop ADHF (Table S4).[28] The beneficial effect of BP reduction on heart failure in SPRINT was consistent with experience in prior trials, including 64%, 50%, and 36% reductions in the HYVET,[29] SHEP,[30] and Syst-Eur[31] trials, respectively. Thus, the SPRINT ADHF result was neither unexpected nor a "soft" outcome as suggested by some observers. [27]

It has also been suggested that the ADHF benefit in SPRINT resulted from differential use of diuretics and masking of underlying heart failure.[27] Only 11 of the 391 participants in whom diuretics were withdrawn at the baseline visit developed ADHF, and this occurred ≦1 month after diuretic withdrawal in only one participant. This represents approximately 6% of the 173 participants who developed ADHF, and an analysis excluding these participants had minimal effect on the estimate of benefit for ADHF prevention in the Intensive group.[32, 33] At the final follow-up visit, 68% of the Intensive and 43% of the Standard group were being treated with a diuretic. Diuretic use during the trial was not a significant predictor of ADHF (HR, 0.96 [0.66–1.40], *P*=0.83).[32] Diuretic use was more, rather than less, prevalent in participants who developed ADHF regardless of treatment arms than in those without ADHF, and most ADHF events occurred in participants who were already

on a prescribed diuretic at the time of their first ADHF diagnosis (Fig S2). Furthermore, separation of ADHF rates between the two treatment groups began after 6 months of follow-up and appeared to increase throughout the trial rather than shortly after medication titration.[28]

Brain Outcomes

Stroke was not significantly reduced in SPRINT (HR:0.89 (0.64, 1.23), but the trial was not powered to assess differences in individual components of the primary outcome. The stroke hazard ratio confidence interval was wide and included a possible 36% reduction in risk (Table 2). In the ACCORD BP trial, stroke was reduced by 41%. However, Kaplan-Meier curves for the stroke outcome did not begin to separate until after 3 years of treatment; this duration is noteworthy since SPRINT was stopped after a median of 3.3 years.[34]

Despite previous concerns about the potential for adverse cognitive effects,[35] intensive BP treatment resulted in a significant reduction in mild cognitive impairment during the trial and a composite of mild cognitive impairment and probable dementia during combined trial and post-trial follow-up (Table 3).[36] Additionally, during a median follow-up of 3.97 years, an MRI sub-study conducted in 670 SPRINT participants reported significantly less progression of cerebral small vessel ischemic disease, as indicated by dense white matter lesions, in the Intensive compared to Standard group.[37] Similar findings were observed in the ACCORD BP trial and post-trial follow-up analysis, and in the INFINITY trial.[38, 39] In SPRINT and ACCORD, a small though significant reduction in total brain volume was noted with intensive treatment, but the clinical significance of this finding is uncertain.

Renal Outcomes:

No difference in the primary kidney disease composite outcome of 50% reduction in estimated glomerular disease rate (eGFR) or end stage renal disease (ESRD) in those with baseline CKD defined as eGFR< 60 ml/min/1.73 m^2 was noted between the two treatment groups (Table 2), but there was limited power for these events. There was a slight average decrease in eGFR in the Intensive arm during the initial six months of therapy in those with (Fig S1) and without CKD (eGFR treatment group difference of 3.3 ml/min/1.).[40, 41] In the Standard arm, a modest acute increase in eGFR in the CKD subgroup and no eGFR change in the non-CKD subgroup was noted. There was no relationship between the early eGFR decrease and CVD outcomes.[42] An acute decline in eGFR has been noted during more intensive antihypertensive treatment in other trials that randomized participants to different BP targets, especially with more preserved renal function.[43, 44] This acute decline in eGFR in the Intensive arm has been attributed to a reversible hemodynamic effect of antihypertensive drug therapy on the renal microcirculation.[45] In both those with and without CKD at baseline, a small annual decline in eGFR of similar magnitude was consistent with the anticipated effects of aging on kidney function, was seen in the two treatment groups after the six month visit. However, the rate of decline was slightly higher in the Intensive than in the Standard arm in the CKD subgroup. In those without CKD at baseline, incident CKD defined as a ≥30% decrease in eGFR and confirmed eGFR ≤60 ml/min/1.73m^2 during follow-up occurred in 4.2% of the Intensive and 1.2% of the Standard groups, but none of the participants developed ESRD and <10% had a decrease in eGFR

≥50% at their final visit.[40 40] Incident albuminuria was significantly less common in the Intensive compared to the Standard group both in those with and without CKD at baseline (Table 2).

Implications of SPRINT for patients with Diabetes Mellitus

SPRINT excluded patients with diabetes, but demonstrated similar treatment benefits in participants with or without pre-diabetes or the metabolic syndrome at baseline.[46, 47] In addition, analyses comparing the effects of intensive and standard BP treatment in ACCORD participants who received standard glycemic therapy have identified benefits similar to those seen in SPRINT.[48–51] Likewise, following discontinuation of the intensive glycemic intervention in the ACCORD BP trial, a pattern of CVD benefit similar to that seen in SPRINT was identified.[51] Thus, SPRINT provides supportive but not definitive evidence on the effect of intensive BP treatment in patients with diabetes.

The J-curve Hypothesis: DBP Reduction and SPRINT Outcomes

J- and U-shaped relationships between DBP and CVD have been identified in some cohort studies[52] and on-treatment analyses of antihypertensive drug treatment trials,[53–55]

influencing treatment recommendations in at least one BP guideline.[21] A fundamentally important question with these J-curve reports is whether the lower BP was the cause or consequence of CVD. A SPRINT on-treatment analysis also identified a U-shaped relationship between baseline DBP and the primary CVD composite outcome as well as all-cause mortality in both the Intensive and Standard groups.[56] However, despite the greater risk of CVD events in those with a lower baseline DBP in both randomized groups, in randomized comparisons both the primary outcome and all-cause mortality were significantly less common in the Intensive compared with the Standard group across all five quintiles of DBP with no suggestion of hazard ratio heterogeneity. These results fail to support an increase in absolute risk based on level of achieved DBP during treatment of hypertension.

Adverse Effects of Intensive Treatment in SPRINT

Detailed procedures for collecting adverse effects, including serious adverse effects (SAEs) were specified in the trial protocol and MOP, particularly related to hypotension, syncope, falls, and acute kidney injury. The Medical Dictionary for Regulatory Activities (MedDRA) was used to classify SAEs. A SPRINT-specific standardized MedDRA with queries for syncope, hypotension, and falls was developed to capture preferred terms under these headings. Adverse events, unlike clinical outcomes, could be collected at any time during the trial. There was no significant difference in overall SAEs between the Intensive and Standard groups (HR=1.04, P=0.25), including in those >75 years old at baseline (HR=1.00, P=0.93).[1, 9, 57] Hypotension, syncope, and falls occurred in 1.7%, 1.8%, and 2.2% of the SPRINT participants, respectively.[57, 58] Compared to the Standard group, the Intensive group had a greater risk of SAE associated with hypotension (2.4% vs. 1.4%, HR=1.67, P=0.002), but the corresponding differences were not significant for syncope (2.3% vs. 1.7%, HR=1.32, P=0.07) or injurious falls (2.2 vs. 2.3%, HR=0.98, P=0.90). For all three outcomes, the hazard ratio for an SAE was higher and nominally significant in the

subgroups with baseline CKD or frailty. Baseline age ≥75 years was also associated with a significantly higher risk of self or provider reported syncope, hypotension, and falls, but not for hospital associated injurious falls. However, there was no age-by-treatment interaction for any of these SAE outcomes.[57] There was no difference in patient reported health-related quality of life measurements, even in participants over 75 years of age.[59]

Acute Kidney Injury (AKI) or Acute Renal Failure (ARF)

AKI or ARF, defined as a hospital admission diagnosis, occurrence during a hospitalization or reported in the hospital discharge summary as a primary or main secondary diagnosis, occurred more often in the Intensive (3.8%) compared with the Standard (2.3%) group (HR=1.66, P<0.001).[60] Of those with adjudicated AKI or ARF events, 78% of participants in the Intensive group and 77% in the Standard group had only KDIGO Stage 1 or 2 severity (identical in those with or without CKD at baseline) and by the end of trial follow-up, 90.4% of the AKI events in the Intensive group and 86.9% in Standard group had completely resolved (serum creatinine within 20% of the participant's baseline value). Partial resolution (creatinine within 30% of the baseline value) was seen in an additional 4.8% of Intensive and 4.0% of Standard group participants with AKI.

Orthostatic Hypotension (OH)

OH (defined as a decrease in SBP ≥20 mmHg or diastolic BP ≥10 mmHg one minute after standing from a seated position) was not a SPRINT exclusion criterion, but individuals with a standing SBP <110 mmHg were not enrolled.[61] OH was present in 7% of the SPRINT participants at baseline and was more frequent in those with a higher seated SBP.[62] During a mean follow-up of 3 years, OH events were noted in 18.5% of the participants and were more common in the Standard (5.7%) compared to Intensive (5.0%) group. In both treatment groups combined, OH was not associated with CVD events (primary outcome: HR=1.06; 95%CI: 0.78 to 1.44) or any secondary outcome.[62] Moreover, OH was not associated with syncope, electrolyte abnormalities, injurious falls, or AKI/ARF. However, OH was associated with hypotension-related hospitalizations or emergency department visits (HR=1.77; 1.11 to 2.82) and bradycardia (HR=1.94; 1.19 to 3.15), but these associations did not differ by BP treatment goal.

Balancing Benefits and Risks of Intensive Treatment

Overall, there was no significant difference in SAEs between the two treatment groups at any age. The SAEs that were significantly more common during Intensive treatment did not lead to an overall increase in major morbidity or mortality. Unlike clinical outcomes which were ascertained only at quarterly protocol visits, SAEs could be reported at any visit including prn visits for BP control and except for the AKI/ARF events were not adjudicated. There were approximately 8% more study visits in the Intensive compared with the Standard group, mostly related to achieving the BP targets, which added opportunities to report adverse events but not trial outcomes (Table S5). Although some authors have done so,[63, 64] the SPRINT hard outcome benefits, including prevention of major CVD and all-cause mortality, and the softer potential adverse events should not be weighted equally. Finally, neither patient-reported health-related quality of life measurements nor gait speed differed by randomized treatment assignment, even in participants over 75 years of age.[59]

Summary/Conclusion

The SPRINT findings indicate that more intensive BP reduction yields substantial health benefits that outweigh the risks of adverse events. The SPRINT design and methods were based on best practices in the conduct of clinical trials, and the trial results were consistent with external evidence. The ability to generalize the SPRINT results to clinical practice requires accurate assessment of BP and evidence of high CV risk. These requirements are common to generalization of other landmark BP treatment trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Forest Plots for Primary Outcome

Subgroup	Intensive	Standard	Hazard Ratio 95% CI	P value for Interaction
Overall	264/4678 (5.64)	354/4683 (7.56)	0.73 (0.63,0.86)	
Pre−Specified				
Age<75	156/3361 (4.64)	196/3364 (5.83)	0.79 (0.64,0.97)	0.24
Age≥75	108/1317 (8.20)	158/1319 (11.98)	0.65 (0.50,0.83)	
Male	179/2994 (5.98)	253/3035 (8.34)	0.70 (0.58,0.85)	0.42
Female	85/1684 (5.05)	101/1648 (6.13)	0.82 (0.61,1.09)	
Black	70/1454 (4.81)	96/1493 (6.43)	0.77 (0.56,1.05)	0.72
Nonblack	194/3224 (6.02)	258/3190 (8.09)	0.72 (0.59,0.86)	
Prior CKD	118/1330 (8.87)	136/1316 (10.33)	0.82 (0.63,1.05)	0.24
No Prior CKD	146/3348 (4.36)	218/3367 (6.47)	0.67 (0.54,0.82)	
Prior CVD	103/940 (10.96)	125/937 (13.34)	0.80 (0.61,1.04)	0.46
No prior CVD	161/3738 (4.31)	229/3746 (6.11)	0.70 (0.57,0.86)	
SBP≤132	77/1583 (4.86)	109/1553 (7.02)	0.67 (0.50,0.90)	0.64
132<SBP<145	85/1489 (5.71)	120/1549 (7.75)	0.74 (0.56,0.98)	
SBP≥145	102/1606 (6.35)	125/1581 (7.91)	0.82 (0.63,1.07)	
Not Pre−Specified				
Hispanic	20/503 (3.98)	26/481 (5.41)	0.62 (0.33,1.15)	0.85
Non−Hispanic Black	64/1379 (4.64)	93/1423 (6.54)	0.71 (0.51,0.98)	
Non−Hispanic White	167/2698 (6.19)	229/2701 (8.48)	0.70 (0.57,0.86)	
Fit	4/159 (2.52)	10/190 (5.26)	0.47 (0.13,1.39)	0.84
Less Fit	48/711 (6.75)	77/745 (10.34)	0.63 (0.43,0.91)	
Frail	50/440 (11.40)	61/375 (16.27)	0.68 (0.45,1.01)	0.30
Prior MetS	105/1737 (6.04)	141/1784 (7.90)	0.75 (0.57,0.96)	0.76
No Prior MetS	146/2807 (5.20)	205/2769 7.40)	0.71 (0.57,0.87)	
Pre−DM	101/1941 (5.20)	144/1957 (7.36)	0.69 (0.53,0.89)	0.30
Normal	142/2721 (5.22)	174/2704 (6.43)	0.83 (0.66,1.03)	

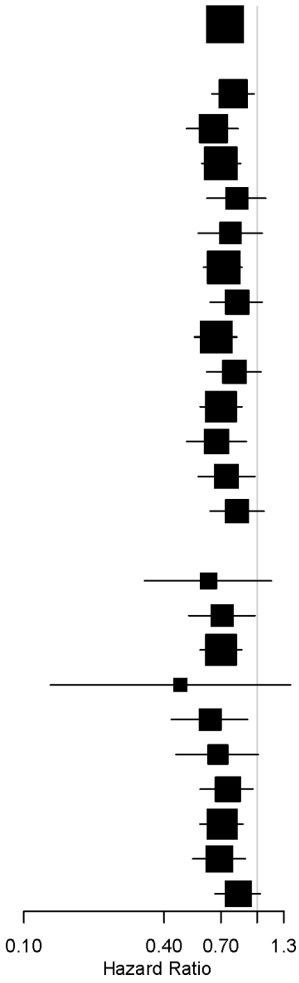

Figure 1.

Primary outcome in prespecified (age, sex, race, and history of cardiovascular disease [CVD] and CKD)[22] and post hoc (Hispanic ethnicity, frailty, metabolic syndrome, and prediabetes) subgroups.[7,9,22,40,46,47]

Forest Plots for All-Cause Mortality

Subgroup	Intensive	Standard	Hazard Ratio 95% CI	P Value for Interaction
Overall	163/4678 (3.48)	215/4683 (4.59)	0.75 (0.61,0.92)	
Pre−Specified				
Age<75	84/3361 (2.50)	107/3364 (3.18)	0.77 (0.58,1.03)	0.77
Age≥75	79/1317 (6.00)	108/1319 (8.19)	0.72 (0.53,0.97)	
Male	114/2994 (3.81)	159/3035 (5.24)	0.72 (0.57,0.92)	0.49
Female	49/1684 (2.91)	56/1648 (3.40)	0.85 (0.58,1.25)	
Black	54/1454 (3.71)	57/1493 (3.82)	0.95 (0.65,1.39)	0.09
Nonblack	109/3224 (3.38)	158/3190 (4.95)	0.66 (0.52,0.84)	
Prior CKD	75/1330 (5.64)	99/1316 (7.52)	0.73 (0.54,1.00)	0.76
No Prior CKD	88/3348 (2.63)	116/3367 (3.45)	0.77 (0.58,1.02)	
Prior CVD	52/940 (5.53)	72/937 (7.68)	0.70 (0.48,1.01)	0.74
No prior CVD	111/3738 (2.97)	143/3746 (3.82)	0.77 (0.60,0.98)	
SBP≤132	48/1583 (3.03)	65/1553 (4.19)	0.68 (0.46,0.99)	0.33
132<SBP<145	44/1489 (2.96)	65/1549 (4.20)	0.70 (0.47,1.02)	
SBP≥145	71/1606 (4.42)	85/1581 (5.38)	0.86 (0.62,1.19)	
Not Pre−Specified				
Hispanic	19/503 (3.78)	12/481 (2.49)	1.58 (0.73,3.62)	0.01
Non−Hispanic Black	51/1379 (3.70)	56/1423 (3.94)	0.92 (0.63,1.35)	
Non−Hispanic White	89/2698 (3.30)	144/2701 (5.33)	0.61 (0.47,0.80)	
Fit	5/159 (3.14)	6/190 (3.16)	0.95 (0.27,3.15)	0.52
Less Fit	26/711 (3.66)	52/745 (6.98)	0.48 (0.29,0.78)	
Frail	40/440 (9.09)	49/375 (13.07)	0.64 (0.41,1.01)	
Prior MetS	60/1737 (3.45)	80/1784 (4.48)	0.74 (0.53,1.04)	0.91
No Prior MetS	98/2807 (3.49)	129/2769 (4.66)	0.76 (0.58,0.99)	
Pre−DM	65/1941 (3.35)	84/1957 (4.29)	0.77 (0.55,1.06)	0.74
Normal	89/2721 (3.27)	125/2704 (4.62)	0.71 (0.54,0.94)	

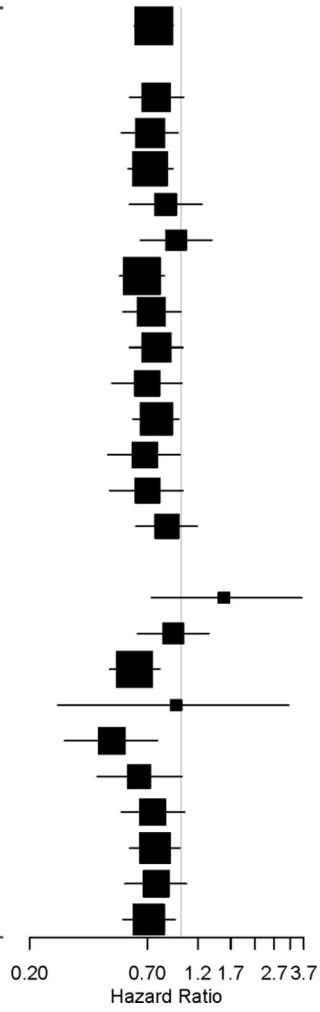

Figure 2.

All-cause mortality outcome in prespecified (age, sex, race, and history of cardiovascular disease [CVD] and CKD)[22] and post hoc (Hispanic ethnicity, frailty, metabolic syndrome, and prediabetes) subgroups. [7,9,22,40,46,47]

Table 1.

Median Follow-Up Systolic Blood Pressures (SBPs) and Median Follow-Up SBPs After 6 Months

Subgroup	Intensive	Standard	Baseline SBP	Median F/U SBPs		Median F/U SBP Δ vs Standard SBP	Median F/U SBP after 6 Months		Median F/U SBP Δ vs Standard SBP after 6 Months
				Intensive	standard		Intensive	standard	
Overall	4678	4683	138.0	120.5	135.1	−14.6	119.2	135.8	−16.6
Pre-Specified									
age<75	3361	3364	138.0	120.0	135.0	−15.0	118.5	135.6	−17.1
age>=75	1317	1319	140.0	122.4	135.5	−13.1	121.2	136.2	−15.0
Male	2994	3035	138.0	120.5	135.0	−14.5	119.0	135.6	−16.6
Female	1684	1648	140.0	120.6	135.4	−14.8	119.3	136.0	−16.7
Black	1454	1493	138.5	120.8	135.6	−14.7	119.4	136.2	−16.9
Nonblack	3224	3190	138.0	120.4	135.0	−14.6	119.1	135.5	−16.4
Prior CKD	1329	1316	138.0	121.7	135.4	−13.7	120.7	136.2	−15.5
No Prior CKD	3349	3367	139.0	120.1	135.1	−15.0	118.6	135.6	−17.0
Prior CVD	940	937	138.0	120.7	134.7	−14.1	119.4	135.5	−16.1
No Prior CVD	3738	3746	139.0	120.5	135.2	−14.7	119.1	135.8	−16.7
Not Pre-Specified									
Fit	178	196	138.0	119.9	135.7	−15.8	118.9	136.3	−17.4
Less Fit	659	680	140.0	122.5	135.2	−12.7	121.4	136.0	−14.6
Frail	474	434	143.0	123.4	135.9	−12.5	121.8	136.4	−14.6
Non-Hispanic White	2698	2701	138.0	120.6	134.9	−14.2	119.3	135.4	−16.2
Non-Hispanic Black	1379	1423	138.0	121.0	135.5	−14.5	119.5	136.2	−16.7
Hispanic	503	481	139.0	118.8	135.3	−16.5	117.7	135.9	−18.2
Prior Metabolic Syndrome	1825	1870	137.0	119.7	134.8	−15.1	118.4	135.2	−16.8
No Prior Metabolic Syndrome	2812	2755	139.0	121.1	135.4	−14.4	119.7	136.1	−16.5
Pre-diabetes	1941	1957	138.0	120.3	135.2	−14.9	119.0	135.7	−16.7
Normal	2721	2704	139.0	120.7	135.1	−14.4	119.2	135.8	−16.5

Median follow-up (F/U) SBP readings (mmHg): medians of 1M, 2M, 3M and quarterly SBP protocol visit readings through to the last visit occurring on or before end of trial intervention (August 20, 2015). Median F/U SBP readings only after 6 months: medians of the quarterly SBP protocol visit readings occurring after and not including the 6-month protocol visit through to the last visit occurring on or before end of trial intervention.

Table 2.

Clinical Outcomes

		Overall		Intensive		Standard			
Sample	**Outcome**	**Events**	**%/yr (95% CI)**	**Events**	**%/yr (95% CI)**	**Events**	**%/yr (95% CI)**	**HR (95% CI)**	**P**
All	Primary outcome (any of A-E)	618	2.08 (1.92, 2.25)	264	1.77 (1.57, 2.00)	354	2.40 (2.16, 2.66)	0.73 (0.63, 0.86)	<0.001
All	(A) All MI	242	0.80 (0.71, 0.91)	102	0.68 (0.56, 0.82)	140	0.93 (0.79, 1.10)	0.72 (0.56, 0.93)	0.01
All	(B) Non-MI ACS	83	0.27 (0.22, 0.34)	42	0.28 (0.20, 0.37)	41	0.27 (0.20, 0.37)	1.02 (0.66, 1.57)	0.93
All	(C) All stroke	147	0.49 (0.41, 0.57)	69	0.45 (0.36, 0.58)	78	0.52 (0.41, 0.64)	0.89 (0.64, 1.23)	0.48
All	(D) All HF	173	0.57 (0.49, 0.66)	68	0.45 (0.35, 0.57)	105	0.70 (0.58, 0.84)	0.63 (0.46, 0.86)	0.003
All	(E) CVD death	112	0.37 (0.31, 0.44)	41	0.27 (0.20, 0.36)	71	0.47 (0.37, 0.59)	0.57 (0.39, 0.84)	0.004
All	Non-fatal MI	240	0.80 (0.70, 0.90)	101	0.67 (0.55, 0.81)	139	0.93 (0.78, 1.09)	0.72 (0.56, 0.93)	0.01
All	Non-fatal stroke	144	0.48 (0.40, 0.56)	68	0.45 (0.35, 0.57)	76	0.50 (0.40, 0.63)	0.90 (0.65, 1.25)	0.53
All	Non-fatal heart failure	167	0.55 (0.47, 0.64)	66	0.43 (0.34, 0.55)	101	0.67 (0.55, 0.81)	0.64 (0.47, 0.87)	0.004
All	All deaths	378	1.24 (1.12, 1.37)	163	1.06 (0.91, 1.24)	215	1.41 (1.23, 1.61)	0.75 (0.61, 0.92)	0.006
All	Primary or death	844	2.84 (2.65, 3.03)	370	2.47 (2.24, 2.74)	474	3.20 (2.93, 3.50)	0.77 (0.67, 0.88)	<0.001
CKD	Primary CKD outcome (any of F-H)	33	0.38 (0.27, 0.54)	17	0.39 (0.24, 0.63)	16	0.37 (0.23, 0.61)	1.02 (0.51, 2.05)	0.95
CKD	(F) 50% reduction in eGFR (2x, ≥90 days apart)	24	0.28 (0.19, 0.42)	12	0.28 (0.16, 0.49)	12	0.28 (0.16, 0.49)	0.97 (0.43, 2.20)	0.95
CKD	(G) Dialysis	17	0.20 (0.12, 0.32)	7	0.16 (0.08, 0.34)	10	0.23 (0.13, 0.43)	0.65 (0.23, 1.70)	0.38
CKD	(H) Kidney transplant	0	-	0	-	0	-	-	
CKD	Incident albuminuria (CKD)	149	4.74 (4.04, 5.57)	64	3.93 (3.08, 5.03)	85	5.61 (4.54, 6.94)	0.71 (0.50, 1.00)	0.05
Non-CKD	Secondary CKD outcome (non-CKD subsample, any of I-K)	189	0.88 (0.76, 1.02)	148	1.39 (1.18, 1.63)	41	0.38 (0.28, 0.51)	3.67 (2.62, 5.26)	<0.001
Non-CKD	(I) 30% reduction in eGFR and <60 (2x, >=90 days apart)	189	0.88 (0.76, 1.02)	148	1.39 (1.18, 1.63)	41	0.38 (0.28, 0.51)	3.67 (2.62, 5.26)	<0.001
Non-CKD	(J) Dialysis	0	-	0	-	0	-	-	
Non-CKD	(K) Kidney transplant	0	-	0	-	0	-	-	
Non-CKD	Incident albuminuria (non-CKD)	326	2.90 (2.60, 3.23)	142	2.54 (2.16, 3.00)	184	3.25 (2.82, 3.76)	0.77 (0.62, 0.96)	0.02

Final results of pre-specified primary and secondary outcomes from SPRINT. *Lewis CE, Fine LJ, Beddhu S, et al. Final cardiovascular and mortality results of a randomized trial of intensive versus standard blood pressure control. N Engl J Med. 2021;384:1921–30*

Table 3.

Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group*

	Treatment Group				
	Intensive		Standard		
Outcomes	**# with Outcomes/ Person-Years**	**Cases/ 1000 person-years**	**# with Outcomes/ Person-Years**	**Cases/ 1000 person-years**	**Hazard Ratio (95% CI)[a] P value**
Probable Dementia	149 / 20,569	7.2	176 / 20,378	8.6	0.83 (0.67 – 1.04) 0.10
Mild Cognitive Impairment	287 / 19,690	14.6	352 / 19,281	18.3	0.81 (0.69 – 0.95) 0.007
Composite of Mild Cognitive Impairment or Probable Dementia	402 / 19,873	20.2	468 / 19,488	24.1	0.85 (0.74 – 0.97) 0.01

*Includes data during trial treatment intervention ending August 20, 2015 and that collected during extended observational follow-up between October 2017 and July 2018. Williamson JD, et al. *JAMA*. 2019;321(6):553–561.