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Blood Pressure Measurement in the Systolic Blood Pressure Intervention Trial (SPRINT)

The Sprint Research Group

Abstract

Recent publications have stated that the blood pressure measurement technique used in SPRINT was unattended. However, the SPRINT protocol does not address the issue of attendance.

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A survey was conducted immediately after SPRINT closeout visits were completed to inquire whether blood pressure measurements were usually attended or unattended by staff.

There were 4082 participants at 38 sites that measured blood pressure after leaving the participant alone the entire time (Always Alone), 2247 at 25 sites that had personnel in the room the entire time (Never Alone), 1746 at 19 sites that left the participant alone only during the rest period (Alone for Rest), and 570 at 6 sites that left the participant alone only during the blood pressure readings (Alone for Blood Pressure Measurement). Similar systolic and diastolic blood pressures within randomized groups were noted during follow-up at the majority of visits in all four measurement categories. In the Always Alone and Never Alone categories, the Intensive group had a similarly reduced risk for the primary outcome compared with the Standard group (Hazard Ratio = 0.62; 95% Confidence Interval: 0.51 to 0.76 and Hazard Ratio 0.64; 95% Confidence Interval: 0.46 to 0.91 respectively; pairwise interaction p value = 0.88); risk was not significantly reduced for the Intensive group in the smaller Alone for Rest and the Alone for Blood Pressure Measurement categories.

Similar blood pressure levels and cardiovascular disease risk reduction were observed in the Intensive group in SPRINT participants whether the measurement technique used was primarily attended or unattended.

Keywords

Blood pressure measurement/monitoring; cardiovascular disease; hypertension; high blood pressure

INTRODUCTION

Hypertension is a major risk factor for coronary heart disease, stroke and kidney failure that affects over one third of Americans and nearly 1.4 billion adults worldwide.¹⁻³ The health risks attributed to increasing blood pressure (BP) appear to be continuous, with no evidence of a BP threshold above a systolic BP of 115 mmHg, with cardiovascular disease (CVD) mortality increasing progressively throughout the range of BP.⁴⁻⁶ There is conclusive evidence that BP lowering reduces the risk of CVD in hypertensive persons, including evidence from the recently published Systolic Blood Pressure Intervention Trial (SPRINT).⁷⁻¹⁰

Knowing how BP is measured is important to understanding BP control and guiding clinicians in appropriate management of hypertension.¹¹ The auscultatory method of BP measurement, which requires staff attendance during the reading, was employed in many landmark hypertension trials and has been the gold standard in clinical practice in the past.^{12, 13} However, concerns have been expressed regarding the safety of mercury sphygmomanometers and the accuracy of auscultatory readings in routine clinical practice. This and convenience of use has led to progressively greater use of automated oscillometric devices in more recent trials.¹²⁻¹⁹ The SPRINT trial used programmable automated oscillometric devices to measure BP, but there is confusion in recent publications from investigators not involved with SPRINT regarding whether the BP measurements at the 102

SPRINT clinical sites were unattended.^{20–23} Concern has also been expressed that the BP readings obtained in SPRINT were not comparable with BP readings in other trials where the measurement was attended and that the intensive treatment goal of <120 mm Hg in SPRINT would actually correspond to higher systolic BP (SBP) values in other trials.²²

To assess whether BP measurements were attended or unattended at SPRINT clinics, we conducted a survey immediately after study closeout to inquire whether site staff were usually in the room with the participant (attended) or not in the room (unattended) during the rest period and/or during the BP measurement. We examined whether there were differences in measured clinic BP, and whether there were corresponding differences in SPRINT major outcome results or safety events, based on staff attendance.

METHODS

Data Availability

Anonymized SPRINT data used in these analyses will be publicly available at the NHLBI Biologic Specimen and Data Repository (BioLINCC) during late 2018 via controlled access at www.biolincc.nhlbi.nih.gov/home.

Study Design

SPRINT was a randomized, controlled, open-label trial that randomized participants to a target systolic BP goal of either <140 mm Hg (Standard) or <120 mm Hg (Intensive). The SPRINT trial was conducted from November 2010 until August 2015 in 102 clinical sites organized into five Clinical Center Networks. The rationale, design, protocol, and main results for SPRINT are publicly available.^{7,16,24} The study was approved by responsible Institutional Review Boards at all participating sites and was registered at ClinicalTrials.gov (NCT 01206062). All participants gave written informed consent and the study conformed to the Declaration of Helsinki and to Title 45, United States, Code of Federal Regulations, Part 46, Protection of Human Subjects.

An independent Data and Safety Monitoring Board (DSMB) monitored trial implementation, unblinded trial results, and safety experiences. Following a recommendation by the trial's DSMB and with the concurrence of the National Heart, Lung, and Blood Institute, the SPRINT BP intervention was halted on August 20, 2015 after a median follow-up of 3.26 years. Follow-up was censored at the date of last assessment for a study event or on August 20, 2015. This publication is based on a database that was frozen on February 8, 2017 and includes outcome events from baseline until the termination of the trial intervention.

Study Population

The eligibility characteristics of the SPRINT participants have been published and can be found in the online supplement. (please see <http://hyper.ahajournals.org> for Supplemental Material)⁷

Interventions

After randomization, SPRINT investigators initiated or adjusted antihypertensive medications to achieve the assigned SBP targets according to a step-care treatment algorithm using antihypertensive drugs approved by U.S. Food and Drug Administration.^{7, 16}

Study BP measurement

All SPRINT sites were provided with the Professional Digital Blood Pressure Monitor (Omron Healthcare, Lake Forest, IL) model 907XL for BP measurement in the trial. A central training session was held in September 2010 and again in March 2014 to train clinic investigators and staff in study procedures. The Clinical Center Networks and Coordinating Center also organized training sessions using conference calls, webinars, and on-site training. Training on BP measurement technique emphasized proper positioning of participants, measurement of arm circumference and use of proper cuff size, and the importance of a 5-minute rest period prior to obtaining the three seated BPs. During the rest and BP measurement periods, the participant was neither completing questionnaires, talking nor texting. The Clinical Center Networks tracked performance of clinical sites and conducted standardized site visits which included assessment of BP measurement.

Additional information about BP measurement technique was also provided to the sites in the SPRINT protocol and SPRINT Manual of Procedures (MOP).^{7, 24, 25} The SPRINT protocol stated that “Seated BP and pulse are measured at each clinic visit after a rest period using an automated device, or manual devices if necessary. The preferred method is the automated device as it offers reduced potential for observer biases and decreased demand on staff in terms of training and effort in data collection.” The SPRINT protocol did not address the issue of staff attendance during the BP measurement. The SPRINT MOP recommended that the staff leave the room during the rest period, but return to take the BPs at the end of the 5-minute rest, but did not require staff attendance or absence during the BP measurement. The Omron Digital Blood Pressure Monitor that was used in SPRINT could be programmed to incorporate the 5-minute rest and then initiate the three BP measurements automatically after the 5 minutes had elapsed. Coordinators were instructed how to program the Omron device during training. The coordinators could have been in or out of the room during the 5-minute rest period and/or during the time the Omron was automatically taking the BP. (please see <http://hyper.ahajournals.org> for Supplemental Material)

Study outcomes

Definitions of study primary outcomes and serious adverse events (SAEs) have been published and can be found in the online supplement. (please see <http://hyper.ahajournals.org> for Supplemental Material)^{7, 16, 24}

Which BP measurement technique used (attended or unattended) in individual SPRINT clinics was not recorded during the trial, but was assessed by a survey immediately after the close-out period (please see <http://hyper.ahajournals.org> for Supplemental Material). In the survey, clinic sites were asked to indicate how often BP measurements were taken at their site when: 1) participants were alone during the 5 minute rest period and also during the 3 BP measurements (Always Alone - AA); 2) study personnel were in the room during the

entire time (Never Alone - NA); 3) participants were alone during the rest period but study staff were present during the 3 BP measurements (Alone for Rest - AR); 4) study personnel were in the room during rest but the participant was alone during the 3 BP measurements (Alone for BP Measurement - ABM) or 5) other. Each clinic was asked to provide a single, consensus response. Based on these responses, 88 sites and participants at each site were placed into one of the four mutually exclusive categories of BP measurement technique (AA, NA, AR, ABM) if they used that technique at least 50% of the time and more than any other. Most sites predominantly used one technique, and after weighting the survey responses by the total number of SPRINT BP examinations performed at each clinic, we calculate that 92% of examinations in AA clinics were performed with staff out of the room for both rest and BP measurements, 82% of examinations in NA clinics were performed with staff in the room for both rest and BP measurements, 85% of examinations in AR clinics were performed with staff out of the room for rest but present for BP measurements, and 89% of examinations in ABM clinics were performed with staff present for rest but out of the room when BP measurements were taken. Fourteen sites (716 participants) that had substantial turnover during the close-out period or that indicated that they did not use any one of the BP measurement techniques 1–4 50% of the time were excluded from these analyses (please see <http://hyper.ahajournals.org> for Supplemental Material). Sites were also asked to rate how confident they were in their response to the BP measurement technique(s) used in their clinic. Of the 88 sites included in these analyses, 83 (94%) indicated they were extremely or very confident in their responses.

Statistical Analysis

BP measurement techniques 1–4 were treated as post-hoc categories for use in participant-level analyses. Standard descriptive statistics (means and standard deviations [SD] for continuous variables; frequencies and percentages for categorical variables) were used unless otherwise noted.

Baseline characteristics were compared by treatment group and BP measurement technique using row-by-column frequency tables for categorical variables and analysis of variance models for continuous variables. We report the p-value for the marginal effect of BP measurement technique after controlling for randomized group, using the Cochran-Mantel-Haenszel statistic for categorical variables and the marginal type III sum of squares for continuous variables. For baseline BPs, we also used general linear models to examine differences between treatment groups and BP measurement techniques after adjustment for age, gender, black race, Hispanic ethnicity, chronic kidney disease (CKD), clinical and subclinical CVD, number of chronic diseases, current and former smoking status, statin use, aspirin use, Framingham risk score, number of BP medications at enrollment, body mass index (BMI), weight, and heart rate.

The mean of the 3 BP measurements (usually obtained from the Omron display) was recorded at visits by the site staff and used for these analyses. We examined average SBP, average diastolic BP (DBP), and average number of medications prescribed during follow-up using mixed linear models. We used contrasts and pairwise comparisons with no adjustment for multiple comparisons to examine differences between techniques.

For CVD and safety outcomes, Cox proportional hazards analyses were used to calculate hazard ratios (HR) with 95% confidence intervals (CI) between treatment groups in each of the 4 BP measurement technique categories. Differences between randomized groups by BP measurement techniques were also examined in adjusted proportional hazard analyses after controlling for the baseline characteristics age, gender, black race, Hispanic ethnicity, CKD, clinical and subclinical CVD, number of chronic diseases, current and former smoking status, statin use, aspirin use, Framingham risk score, SBP and DBP, number of BP medications at enrollment, BMI, weight, and heart rate. In both adjusted and unadjusted models, contrasts were used to compare hazard ratios between the AA and NA categories.

We also performed several sensitivity analyses, including analyses repeated after collapsing the BP measurement techniques into two categories, attended (NA + AR) vs. unattended (AA + ABM) blood pressure measurements, analyses repeated after restricting classification of BP techniques to sites using that technique for at least 85% of BP exams, and models for blood pressures and prescribed medications fit separately for each visit. Results of these analyses are presented in the online supplement (please see <http://hyper.ahajournals.org>).

RESULTS

SPRINT randomized 9,361 participants to either the Intensive or Standard arm. A total of 38 sites (4082 participants) were classified to the AA category, 25 sites (2247 participants) were classified to the NA category, 19 sites (1746 participants) were classified to the AR category, and 6 sites (570 participants) were classified to the ABM category (please see <http://hyper.ahajournals.org> for Supplemental Material). Thus, a total of 44 sites with 3,993 participants had BP measured while the staff were in the room (attended, NA + AR), and 44 sites with 4652 participants had BP measured while the staff were out of the room (unattended, AA + ABM). (Figure 1 Consort Diagram).

Analyses of the baseline participant characteristics for the four BP measurement technique categories by treatment assignment revealed significant differences (Table 1 and please see <http://hyper.ahajournals.org> for Supplemental Material Tables S1 and S2). The participants in the NA and ABM categories were younger; the participants in ABM category were more likely to be Hispanic, female, and a non-smoker and less likely to use statin or aspirin therapy; the participants in the AA category were more likely to have CKD; the participants in the AA and NA categories were more likely to have CVD and have a higher Framingham risk score; and the participants in the NA category were most likely to be a current smoker. Both the Intensive and Standard treatment groups in the ABM category had higher average SBP readings (p value =0.001) and lower DBP readings (p value <0.001) at baseline compared with the other BP measurement technique categories (Table 1). After adjustment for other variables listed in Table 1, the DBP readings at baseline remained lowest in the ABM category (p value <0.001). The baseline SBP differences were attenuated but remained significantly different, with the NA group having lower average SBP than the other groups (mean adjusted SBPs were 139.1 mm Hg in the NA group vs. 139.9, 140.2, and 139.9 mm Hg in the AA, AR and ABM groups, respectively, p = 0.049)

Average BPs over time are presented by treatment group and BP measurement technique category in Figure 2, Table 2, and Supplemental Tables S3 and S4 (please see <http://hyper.ahajournals.org>). The post-randomization differences in average SBP and DBP among the 4 BP measurement technique categories in the Intervention arm were relatively small (SBP range 120.6 – 122.2 mm Hg and DBP range 67.4 – 68.3 mm Hg respectively). A similar finding was noted for the 4 BP measurement technique categories in the Standard group (SBP range 134.4 – 135.4 and DBP range 73.0 – 75.0 respectively) (Table 2). At the majority of follow-up visits, similar SBPs within randomized groups were noted among participants in all four BP measurement technique categories. Heterogeneity in treatment effect by BP measurement technique was detected for SBP at only the 27-month visit (interaction p value = 0.020). Similarly, no heterogeneity of treatment effect was detected for DBP by BP measurement technique category through month 24 of follow-up. In a sensitivity analysis, average SBP and DBP by treatment group over time for attended (NA + AR) blood pressure measurement was also compared with unattended (AA + ABM) measurement and revealed essentially no difference whether the staff were in the room or not (attended Intensive SBP mean = 121.5 mm Hg compared with unattended Intensive SBP mean = 121.5 mm Hg and attended Standard SBP mean = 134.5 mm Hg compared with unattended Standard SBP mean = 134.7 mm Hg, all p values > 0.05) Additional information on BP is available in Supplemental Tables S5 and S6) (please see <http://hyper.ahajournals.org>)

Average medication use over time is presented by treatment group and BP measurement technique categories in Table 2, and Supplemental Table S7 (please see <http://hyper.ahajournals.org>). At the majority of follow-up visits, similar average number of medication use within randomized groups was noted among participants in all four BP measurement technique categories.

When the larger AA and NA groups were compared with one another, there was no evidence of heterogeneity of treatment effect by BP measurement technique for the primary outcome (pairwise interaction p-value = 0.88). However, when all four measurement technique categories were compared, heterogeneity of treatment effect was detected for the primary outcome (interaction p-value = 0.005) (Table 3). In both the AA and NA categories the Intensive treatment group had a reduced risk of the primary outcome compared to the Standard treatment group (HR = 0.62; 95% CI: 0.51 to 0.76 and 0.64; 95% CI: 0.46 to 0.91 respectively); however, no significant difference between the treatment groups among participants in the smaller AR and the ABM categories was detected.

No heterogeneity of treatment effect was detected for total mortality by BP measurement technique (interaction p-value = 0.28) (Table 3). In the AA and AR categories, the Intensive group compared to the Standard group had a reduced risk of total mortality (HR= 0.65; 95% CI: 0.47 to 0.88 and HR= 0.59; 95% CI: 0.37 to 0.94 respectively). A similar point estimate of reduced risk for total mortality in the Intensive group compared to the Standard group was seen in the NA category. No difference between the Intensive and Standard groups in total mortality was detected in the much smaller ABM category (Table 3). When only the larger AA and NA groups are compared to one another, no evidence of heterogeneity of treatment effect by BP measurement technique was detected (interaction p-value = 0.51). In both

categories the Intensive treatment group had a reduced risk of total mortality compared to the Standard treatment group.

Since there were substantial differences in baseline characteristics by BP measurement technique, Cox proportional hazards analyses for the primary outcome and total mortality adjusted for the baseline variables listed in Table 1 were conducted. After adjustment, the heterogeneity of treatment effect by BP measurement technique for the primary outcome remained significant (interaction p-value = 0.008). Similar to the unadjusted analyses, the adjusted analyses showed no significant heterogeneity of treatment effect by BP measurement technique for total mortality (interaction p-value = 0.42) (Supplemental Table S8; please see <http://hyper.ahajournals.org>).

Additional sensitivity analyses were conducted in clinics that used the BP measurement technique 85% of the time and no heterogeneity of treatment effect was detected for the primary outcome or for total mortality (Supplemental Tables S9 and S10; please see <http://hyper.ahajournals.org>).

There was no difference in total SAEs between the Intensive and Standard groups in any of the four BP measurement technique categories (Table 4). Further, we could not detect no significant heterogeneity of treatment effect for total SAEs (interaction p-value = 0.57) or for any of the other monitored conditions of interest (syncope, hypotension, injurious falls, bradycardia, acute kidney injury, or electrolyte abnormality) by BP measurement technique (all other interaction p-values > 0.05). In a model adjusting for the baseline characteristic differences by BP measurement technique, the findings did not substantially change in SAEs or other monitored conditions. (Supplemental Table S11; please see <http://hyper.ahajournals.org>).

DISCUSSION

Blood pressure in SPRINT was measured in a standardized method in both attended and unattended conditions. Similar SBP differences (12–14 mm Hg) between the Intensive and Standard groups were seen in all four BP measurement technique categories regardless of staff attendance and these differences were well maintained over the course of the trial. Overall, there was no compelling evidence in SPRINT that unattended BP measurements, as in the AA (always alone) category, led to lower SBP at baseline or during follow-up, compared to the NA (never alone) category. In addition to similar SBP differences between randomized groups, the AA and NA categories had very similar mean SBP values (with only 1–2 mm Hg difference) at baseline and throughout follow-up, but this does not rule out a true BP difference between the groups.

SPRINT BP measurements were conducted using methods that were commonly recommended by professional societies and BP guidelines committees at the time the trial started.^{14, 26–28} These recommendations emphasized the importance of the BP measurement methods, but did not state whether the patient should be attended or unattended.¹⁴ Other trials using automatic BP monitors used standardized techniques such as those used in SPRINT, but SPRINT is the first clinical outcome trial where the issue of staff presence or

absence during measurement and the effect on obtained BP values has been questioned.
17, 22, 29

SPRINT data presented in this report contradict assumptions that all BP measurements taken in SPRINT were unattended and thus cannot be directly compared with other trials where BP measurement was attended.²² A corollary is that these SPRINT data also do not support the suggestion that the intensive treatment goal of <120 mm Hg in SPRINT would actually correspond to substantially higher SBP values in other trials where the BP measurement was assumed to be attended.²² Data from the SPRINT Ambulatory Blood Pressure Ancillary Study (n=897) also support the contention that the BP values obtained at the SPRINT study clinic visit whether attended or unattended are similar to values obtained during 24-hour ambulatory blood pressure monitoring.³⁰

The present SPRINT data are inconsistent with several published reports suggesting that BP values were lower when taken unattended compared to attended BP measurements.^{31–33} However, many of these previous reports were comparisons of non-standardized office BP or home BP measured with the patient's device compared with standardized automated unattended BP measurements, where many differences such as patient positioning and rest periods in addition to staff attendance are likely to have played a role in the reported BP differences. Additional research, with more controlled environments, is needed to determine whether and to what extent attendance during the BP measurement affects level of BP.

CVD and total mortality risk were reduced similarly in participants treated to the Intensive compared with Standard goals in clinics using either the NA and AA BP measurement techniques, with no evident increased risk of SAEs related to whether BP measurements were attended or unattended. Furthermore, if attendance during the BP measurement led to higher BP readings compared to unattended measurement, then participants in the Intensive arm in the NA category would have been expected to have been prescribed more medication, possibly resulting in increased SAEs such as syncope or hypotension compared to participants in the intensive arm of the AA category. However, the average number of medications used was not different between these two categories, and there was no difference in overall rates of SAEs, syncope, or hypotension. Thus, it does not appear that attendance at BP measurement sessions in SPRINT led to over-treatment using the SPRINT BP treatment algorithm.

These analyses suggest that using the SPRINT Intensive treatment algorithm and a SBP goal of <120 mm Hg, along with the BP measurement techniques recommended by hypertension guideline committees including use of a validated automated BP device in clinical practice in persons at high risk for CVD, will reduce the risks of CVD and mortality to a similar degree whether the BP measurement is attended or unattended. Furthermore, these findings suggest that staff training to allow for a quiet rest period, proper positioning of the arm and body, use of proper cuff size, and multiple measurements using a validated automated BP device may be more important than whether the BP measurement is attended or unattended.

Not surprisingly, there were baseline differences in the characteristics of participants in the four BP measurement categories as SPRINT did not systematically assign individuals to

these categories and made substantial efforts to recruit a diverse group of qualified participants. Of note, the ABM category was much smaller with fewer events compared to the other three BP measurement categories, which could have resulted in less stable risk estimates than in the much larger AA and NA categories.

The strengths of SPRINT include its large sample size, diverse participant population, success in both implementing the protocol and achieving the SBP targets and sustained mean difference in SBP between the two treatment groups throughout the trial, and the robust CVD and mortality outcome differences. Another strength of SPRINT was central staff training, quality assurance monitoring, and use of a validated automated electronic sphygmomanometer, which may have improved standardization and reduced bias.

Limitations of these analyses include use of a post-hoc survey to assess the BP measurement technique, and classifications based on staff recall rather than real-time individual evaluation of staff attendance before and during the BP readings. In addition, staff turnover during the trial may have contributed to incomplete data collection or inaccurate recall of the BP measurement technique used. Thus, there is a potential for misclassification and responses by staff that were socially desirable, which may have influenced the results towards null findings. However, we believe that misclassification was minimal because the majority of study coordinators at each of the clinics reported performing the same BP measurement technique on the majority of occasions with a high level of confidence in their report.

Another limitation of these data includes the fact that both unattended and attended BP measurements were not made in the same individual participant at the same time. Thus, a direct comparison of attended and unattended BP measurement technique in the same individual cannot be made from the SPRINT data, and this question will require future study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PERSPECTIVES

Similar BP levels and CVD risk reduction were observed in SPRINT participants whether the BP measurement technique used was primarily attended (NA) or unattended (AA). To arrive at firmer conclusions, additional research with better methods, is needed to determine whether attendance or other factors during the BP measurement affect level of BP reading.

NOVELTY AND SIGNIFICANCE

What is new?

- Similar BP levels and CVD risk reduction were observed in the Intensive group in SPRINT participants whether the BP measurement technique used was primarily attended or unattended.

What is relevant?

- In order to fully realize the benefits and minimize risks associated with following the SPRINT Intensive treatment algorithm, use of a validated automated BP device, staff training to allow for a quiet rest period, proper positioning of the arm and body, use of proper cuff size, and averaging multiple measurements may be more important than whether the BP measurement is attended or unattended.

Summary

These SPRINT data appear to contradict assumptions that BP taken in SPRINT cannot be directly compared with BP in other trials.

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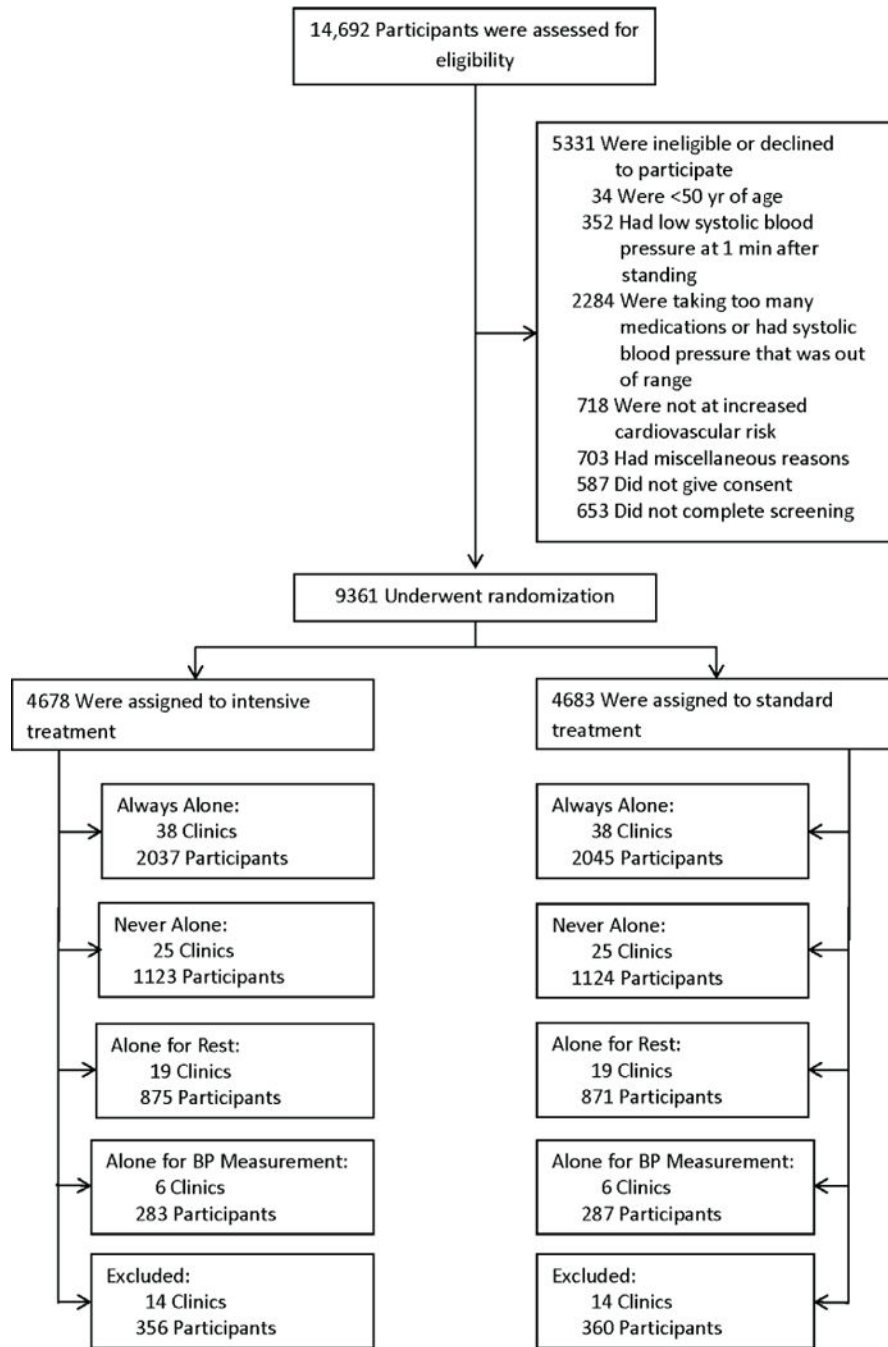


Figure 1.
CONSORT diagram

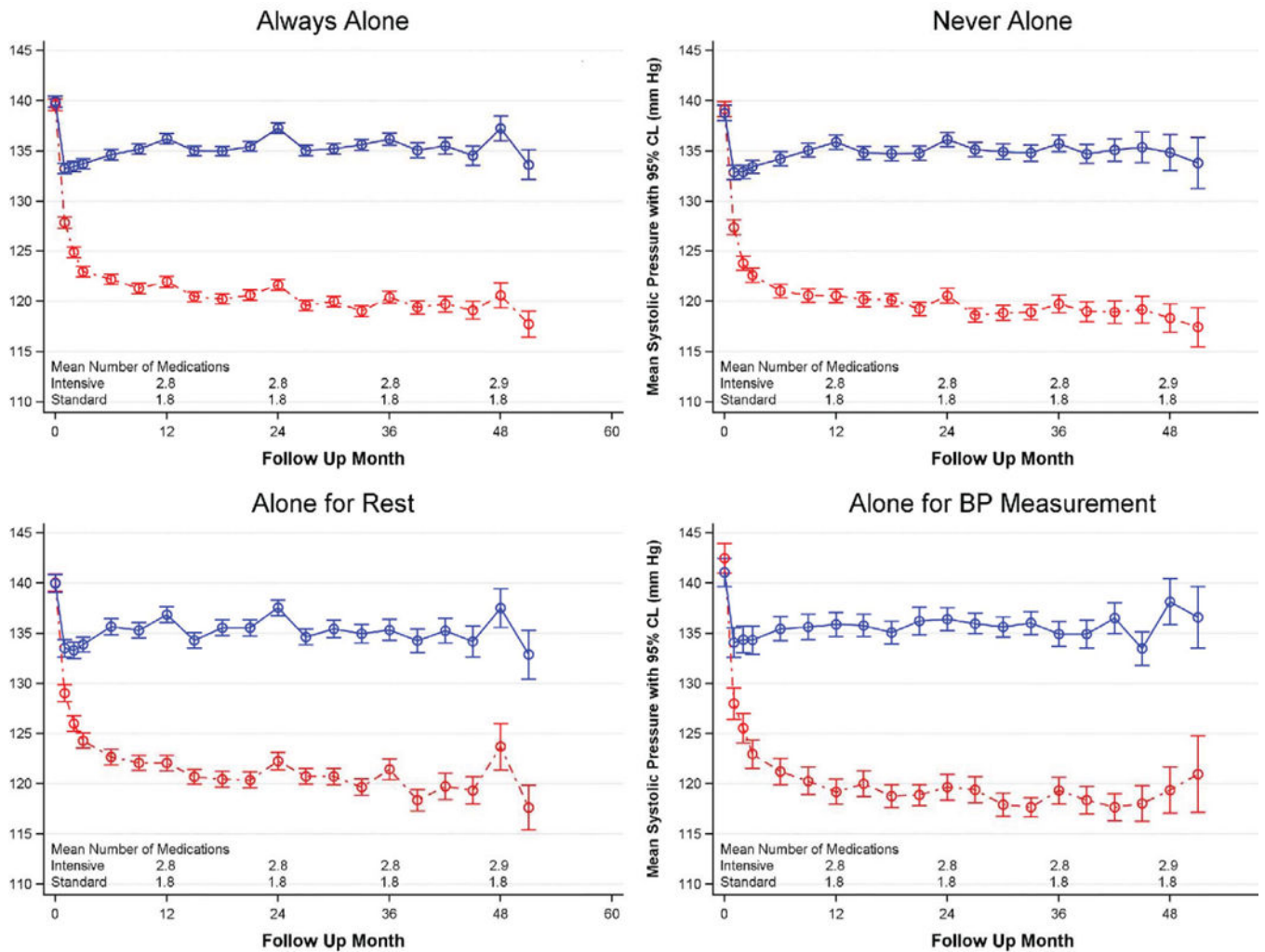


Figure 2. Systolic Blood Pressure by BP Measurement Technique Reported by SPRINT Staff over Time. Means and confidence intervals for standard group participants are shown in blue, while those for intensive group participants are shown in red.

Table 1
Baseline Characteristics of SPRINT Participants Stratified by Randomized Group and Blood Pressure Technique

Characteristics	Always Alone (n =4082)		Never Alone (n =2247)		Alone for Rest (n =1746)		Alone for BP Measurement (n=570)		P value*
	Intensive	Standard	Intensive	Standard	Intensive	Standard	Intensive	Standard	
No. Clinics	38		25		19		6		
No. Randomized	2037 (100)	2045 (100)	1123 (100)	1124 (100)	875 (100)	871 (100)	283 (100)	287 (100)	
Age 50–64	730 (35.8)	767 (37.5)	565 (50.3)	552 (49.1)	303 (34.6)	296 (34.0)	132 (46.6)	130 (45.3)	
65–74	674 (33.1)	656 (32.1)	298 (26.5)	290 (25.8)	286 (32.7)	287 (33.0)	93 (32.9)	104 (36.2)	<0.001
75	633 (31.1)	622 (30.4)	260 (23.2)	282 (25.1)	286 (32.7)	288 (33.1)	58 (20.4)	53 (18.5)	
Female Gender	668 (32.8)	620 (30.3)	340 (30.3)	349 (31.0)	351 (40.1)	376 (43.2)	138 (48.8)	139 (48.4)	<0.001
Black Race	595 (29.2)	625 (30.6)	409 (36.4)	419 (37.3)	244 (27.9)	228 (26.2)	81 (28.6)	78 (27.2)	<0.001
Hispanic Ethnicity	64 (3.1)	45 (2.2)	193 (17.2)	182 (16.2)	26 (3.0)	26 (3.0)	183 (64.7)	187 (65.2)	<0.001
Chronic kidney disease‡	633 (31.2)	633 (31.0)	282 (25.1)	270 (24.0)	254 (29.0)	254 (29.2)	57 (20.1)	67 (23.3)	<0.001
Cardiovascular disease	438 (21.5)	448 (21.9)	238 (21.2)	237 (21.1)	145 (16.5)	144 (16.5)	54 (19.1)	51 (17.8)	<0.001
Clinical	276 (13.6)	279 (13.6)	154 (13.7)	151 (13.4)	84 (9.6)	81 (9.9)	27 (9.5)	23 (8.0)	<0.001
Subclinical	174 (8.5)	178 (8.7)	87 (7.8)	100 (8.9)	51 (5.8)	58 (6.7)	38 (13.4)	35 (12.2)	<0.001
Framingham 10-yr CVD risk score-%	25.8±12.9	26.0±12.5	25.1±13.1	24.8±12.8	24.0±11.5	23.8±11.9	23.6±12.8	22.5±11.5	<0.001
SBP, mmHg	139.6±15.9	139.9±15.2	139.2±15.8	138.8±15.3	140.0±15.2	140.0±15.9	142.5±15.0	141.1±14.4	0.001
DBP, mmHg	77.9±11.6	78.0±12.0	79.3±12.1	78.7±11.6	77.8±12.1	77.1±12.8	76.9±11.0	76.2±10.5	<0.001
Pulse, bpm	65.9±11.7	66.1±12.2	66.6±11.2	66.7±11.7	66.4±12.0	65.5±10.9	65.8±10.1	67.0±10.2	0.11
# of BP Medications	1.9±1.0	1.9±1.0	1.9±1.0	1.9±1.0	1.7±1.1	1.7±1.1	1.7±1.0	1.6±0.9	<0.001
Weight, lbs.	192.2±41.5	193.8±41.8	194.0±40.4	191.0±40.7	186.3±41.4	186.2±42.1	183.4±38.2	181.5±38.2	<0.001
BMI, Kg/m ²	30.0±5.8	29.9±5.7	30.2±5.7	29.9±5.7	29.3±5.6	29.2±5.7	29.6±5.2	29.4±5.0	<0.001
# of Chronic Diseases	2.8±1.7	1.8±1.7	2.6±1.7	2.6±1.7	2.7±1.7	2.7±1.7	2.2±1.5	2.2±1.5	<0.001
Smoking Status									
Current	271 (13.3)	256 (12.6)	189 (16.9)	165 (14.7)	85 (9.7)	96 (11.1)	37 (13.1)	33 (11.5)	<0.001
Past	919 (45.2)	911 (44.7)	469 (41.9)	472 (42.1)	356 (40.8)	389 (44.8)	97 (34.3)	79 (27.6)	<0.001
Statin use	935 (46.3)	938 (46.3)	458 (41.0)	497 (44.5)	358 (41.1)	382 (44.2)	97 (34.4)	113 (39.8)	<0.001
Aspirin use	1106 (54.6)	1116 (54.8)	574 (51.2)	553 (49.2)	442 (50.5)	415 (47.8)	103 (36.4)	107 (37.4)	<0.001

* Test for differences among BP measurement techniques after controlling for randomized group assignment. Cardiovascular disease (CVD), blood pressure (BP), body mass index (BMI)

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Table 2

Average post-randomization blood pressures and medications, controlling for subject, visit and clinical site

Variable	Always Alone	Never Alone	Alone for Rest	Alone for BP Measurement
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Systolic BP				
Intensive Participants	121.4 (120.7, 122.0) ^a	121.0 (120.2, 121.8) ^a	122.2 (121.3, 123.1) ^a	120.6 (119.1, 122.2) ^a
Standard Participants	134.4 (133.8, 135.1) ^a	134.4 (133.6, 135.1) ^a	134.7 (133.8, 135.6) ^a	135.4 (133.8, 136.9) ^a
Delta	13.1 (12.6, 13.5) ^a	13.3 (12.7, 13.9) ^a	12.5 (11.9, 13.2) ^a	14.7 (13.5, 15.9)
Diastolic BP				
Intensive Participants	67.9 (66.9, 69.0) ^a	68.3, (67.0, 69.6) ^a	67.4 (65.9, 68.9) ^a	68.0 (65.4, 70.6) ^a
Standard Participants	74.6 (73.6, 75.7) ^a	75.0 (73.7, 76.3) ^a	74.0 (72.5, 75.5) ^a	73.0 (70.4, 75.7) ^a
Delta	6.7 (6.2, 7.2) ^a	6.7 (6.0, 7.4) ^{ab}	6.6 (5.8, 7.3) ^{ab}	5.0 (3.7, 6.4) ^b
Number of Medications				
Intensive Participants	2.7 (2.7, 2.8) ^{ab}	2.8 (2.7, 2.9) ^b	2.7 (2.6, 2.8) ^a	2.5 (2.4, 2.7) ^a
Standard Participants	1.8 (1.8, 1.9) ^a	1.9 (1.8, 2.0) ^a	1.8 (1.7, 1.9) ^a	1.8 (1.6, 1.9) ^a
Delta	0.9 (0.8, 1.0) ^a	0.9 (0.9, 1.0) ^a	0.9 (0.8, 1.0) ^a	0.8 (0.6, 0.9) ^a

* Within rows, cells with the superscript "a" are not different ($p > 0.05$) from other cells with the superscript "a" or "ab", but are different ($p < 0.05$) from cells with the superscript "b" or with no superscript at all. Similarly, within rows cells with the superscript "b" are not different ($p > 0.05$) from other cells with the superscript "b" or "ab" but are different ($p < 0.05$) from cells with the superscript "a" or with no superscript at all.

Table 3
Primary and all-cause mortality outcomes stratified by treatment group and blood pressure technique

Outcome	Intensive Arm			Standard Arm			Intensive vs. Standard Hazard Ratio			Interaction P-value
	N	Events	% Per year	N	Events	% Per year	HR	95% CI		
Primary	BP Technique	2037	101	1.5	2045	159	2.5	0.62	0.51,0.76	0.005
	Always Alone	1123	68	1.9	1124	103	3.0	0.64	0.46,0.91	
	Never Alone	875	50	1.8	871	51	1.9	0.98	0.76,1.25	
	Alone for Rest	283	20	2.1	287	15	1.5	1.39	0.78,2.49	
All death	Always Alone	2037	64	1.0	2045	98	1.5	0.65	0.47,0.88	0.28
	Never Alone	1123	46	1.3	1124	60	1.7	0.76	0.53,1.11	
	Alone for Rest	875	19	0.7	871	32	1.1	0.59	0.37,0.94	
	Alone for BP Measurement	283	10	1.0	287	7	0.7	1.48	0.63,3.05	

SAE and other monitored adverse event outcomes stratified by treatment group and blood pressure technique

Table 4

Outcome	Intensive Arm			Standard Arm			Intensive vs. Standard Hazard Ratio		
	N	Events	% Per year	N	Events	% Per year	HR	95% CI	Interaction P-value
Any SAE	2037	814	15.4	2045	793	15.0	1.03	0.95,1.12	0.57
	1123	428	14.7	1124	419	14.3	1.02	0.85,1.23	
Always Alone	875	330	14.6	871	333	14.8	0.99	0.88,1.10	
Never Alone	283	73	8.9	287	67	7.7	1.16	0.96,1.41	
Alone for BP Measurement	2037	52	0.8	2045	29	0.4	1.79	1.20,2.68	0.14
Always Alone	1123	18	0.5	1124	15	0.4	1.19	0.61,2.34	
Never Alone	875	14	0.5	871	17	0.6	0.82	0.46,1.46	
Alone for Rest	283	4	0.4	287	6	0.6	0.68	0.11,4.42	
Always Alone	2037	45	0.7	2045	26	0.4	1.73	1.03,2.92	0.48
Never Alone	1123	25	0.7	1124	10	0.3	2.50	1.30,4.78	
Alone for Rest	875	16	0.6	871	13	0.5	1.22	0.55,2.71	
Always Alone	283	3	0.3	287	5	0.5	0.61	0.04,9.99	
Never Alone	1123	27	0.8	1124	28	0.8	0.95	0.57,1.59	0.64
Always Alone	2037	42	0.6	2045	38	0.6	1.10	0.66,1.84	
Never Alone	875	19	0.7	871	23	0.8	0.82	0.49,1.38	
Alone for Rest	283	5	0.5	287	2	0.2	2.59	0.40,16.76	
Always Alone	2037	36	0.5	2045	31	0.5	1.15	0.74,1.81	–
Never Alone	1123	18	0.5	1124	17	0.5	1.05	0.60,1.84	
Alone for Rest	875	12	0.4	871	17	0.6	0.70	0.31,1.58	
Always Alone	283	4	0.4	287	0	0	–	–	
Never Alone	1123	46	1.3	1124	22	0.6	2.08	1.16,3.75	
Alone for Rest	875	30	1.1	871	14	0.5	2.15	1.22,3.77	
Always Alone	283	8	0.8	287	7	0.7	1.18	0.62,2.26	
Never Alone	2037	66	1	2045	48	0.7	1.38	1.04,1.83	0.38
Alone for BP Measurement	1123	22	0.6	1124	24	0.7	0.91	0.50,1.67	

Outcome	Intensive Arm			Standard Arm			Intensive vs. Standard Hazard Ratio		Interaction P-value
	N	Events	% Per year	N	Events	% Per year	HR	95% CI	
BP Technique									
Alone for Rest	875	28	1	871	19	0.8	1.47	0.80,2.72	
Alone for BP Measurement	283	6	0.6	287	2	0.2	3.10	0.78,12.38	