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Comparison of Frequency of Atherosclerotic Cardiovascular and Safety Events With Systolic Blood Pressure < 120 mm Hg Versus 135–139 mm Hg in a Systolic Blood Pressure Intervention Trial Primary Prevention Subgroup

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Abstract

Whether the benefit of intensive blood pressure (BP) control reduces atherosclerotic cardiovascular disease (ASCVD) risk without increasing risks of serious adverse events (SAEs) is unknown. We sought to assess differences in incident ASCVD and SAE with intensive BP control across the spectrum of 10-year ASCVD risk in the Systolic Blood Pressure Intervention Trial (SPRINT). SPRINT randomized 9,361 participants who were ≥50 years old and ≥1 CVD risk factor to standard or intensive BP control (<120 or 130 to 139 mm Hg). We excluded adults with clinical ASCVD or age ≥80. We included 6,875 participants. We compared hazard ratios (HR) and risk differences (RD) of incident ASCVD events or SAEs in all and across quartiles of baseline risk. Median predicted ASCVD risk was 15.9%. Intensive BP control significantly reduced ASCVD events (HR 0.75, 95% confidence interval 0.58, 0.97, $p = 0.03$; RD -0.94; -1.8, -0.1; $p = 0.03$). There was no difference in effect across quartiles of ASCVD risk. There was a non-significant increase in SAE with intensive BP control (HR 1.08, 1.00, 1.17 $p = 0.06$; RD 2.1, -0.1, 4.4, $p = 0.03$), and no difference in this effect across quartiles of risk. In SPRINT participants without baseline clinical ASCVD, the benefit of intensive BP control for primary prevention of ASCVD may extend to lower risk participants without an increase in SAE. In conclusion, lower

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Declarations of Interest

Dr. Appel reports serving as the chair of the SPRINT data safety monitoring board. Other authors have no other relevant disclosures.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.06.041.

risk adults with stage 1 hypertension meeting SPRINT eligibility may benefit from initiation of antihypertensives.

In this secondary analysis of a primary prevention subgroup of the Systolic Blood Pressure Intervention Trial (SPRINT),¹ we sought to understand if the benefits of intensive blood pressure (BP) control extend to those with low predicted atherosclerotic cardiovascular disease (ASCVD) risk without increasing harm. We examined changes in the relative risk and risk difference (RD) for ASCVD events and serious adverse events (SAEs) across baseline ASCVD risk. We hypothesized that level of baseline risk would be predictive of incident ASCVD events and intensive BP control would demonstrate a greater absolute and relative risk reduction in those with higher baseline risk while increasing SAEs.

Methods

Detailed methods of SPRINT appear elsewhere.^{1,2} Adults aged ≥ 50 years with systolic BP ≥ 130 mm Hg and ≥ 1 cardiovascular disease (CVD) risk factor, but without a history of diabetes mellitus or stroke, were recruited at 102 sites in the United States and Puerto Rico between 2010 and 2013. Participants were randomized in a 1:1 ratio to standard BP control (systolic BP 135 to 139 mm Hg) or intensive BP control (systolic BP <120 mm Hg) in an open-label fashion. The trial was stopped early in August 2015 for mortality benefit in the intensive BP control arm.

We used a de-identified database based on the SPRINT trial primary outcome report downloaded from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repositories Information Coordinating Center (BioLINCC) website (<https://biolincc.nhlbi.nih.gov/>). Since estimated 10-year ASCVD risk is used in primary prevention, we excluded individuals with clinical ASCVD at baseline.³ We also excluded those with missing data for Pooled Cohort Equation (PCE) estimation and those with age ≥ 80 years old as the PCE has not been validated for this group.⁴ We included patients with chronic kidney disease as current guidelines recommend lower BP targets to prevent progression of chronic kidney disease, not prevention of ASCVD events. We estimated baseline 10-year ASCVD risk with the PCE using age, gender, race, total cholesterol, high-density lipoprotein cholesterol, systolic BP, receipt of antihypertensive medications, and smoking status.

Follow-up data included efficacy and safety outcomes over the course of 54 months, the maximum duration of follow-up. The primary efficacy outcome was a composite of reported incident ASCVD events, including CVD death but not including peripheral artery disease or abdominal aortic aneurysm-related outcomes as these endpoints were not provided. In contrast to the primary composite outcome in SPRINT, we did not include heart failure (HF) since the PCE equation was not developed using this outcome. Specifically, the components of ASCVD events were myocardial infarction, nonmyocardial infarction acute coronary syndrome, stroke, or CVD death. The primary safety outcome was SAEs. Adverse events were defined as untoward or unfavorable medical occurrences with abnormal, clinically-significant signs, symptoms, or disease associated with research participation, regardless of its consideration as potentially related to participation. SAEs were any adverse events that

were fatal or life-threatening events leading to significant or persistent disability requiring hospitalization, resulting in a congenital anomaly or birth defect, or important medical events believed to represent significant hazards or harms to participants potentially requiring an intervention to prevent hospitalization, permanent disability, or death.⁵

The Johns Hopkins University and University of Vermont Institutional Review Boards determined that this research was exempt from committee review. Analyses were performed on an intention-to-treat basis using Stata 14.2 MP (StataCorp, College Station, Texas). A 2-tailed $p < 0.05$ was considered statistically significant.

Summary statistics were calculated for all participants by quartile of baseline 10-year ASCVD risk. We confirmed that each model using Cox proportional hazards did not violate the proportional hazards assumption by assessing Schoenfeld residuals. To assess the association between baseline 10-year ASCVD risk and the outcomes of interest, we calculated hazard ratios (HRs) for each outcome using baseline 10-year ASCVD risk as a continuous independent variable. Harrell's C-statistic assessed for discrimination.⁶ As there were fewer than 10 years of follow-up in SPRINT, we were unable to assess calibration. Visualization of the relationships between level of baseline 10-year ASCVD risk and relative hazard of ASCVD events and SAEs was performed using restricted cubic spline models with 95% confidence intervals (CIs) relative to the median.⁷ Kernel density plots visualized the distribution of baseline 10-year ASCVD risk levels in those with and without events of interest.

We calculated cumulative incidence for ASCVD events and SAEs by quartile of risk then calculated HRs comparing intensive versus standard BP control for incident ASCVD events and SAEs for the entire sample and by baseline 10-year ASCVD risk quartile. Effect modification by risk quartile and treatment arm was assessed via interaction terms. We used generalized linear models for the binomial family to calculate risk difference (RD) for all participants and by quartile of risk. We assessed for effect modification by risk quartile and treatment arm using an interaction term. A sensitivity analysis incorporating hypertension guideline recommendations compared HRs and RDs for ASCVD events and SAEs in those with 10-year ASCVD risk $< 10\%$ and those with 10-year ASCVD risk $\geq 10\%$.

Results

Of the 9,361 participants with follow-up data, 1,277 were excluded for baseline ASCVD, 883 for age ≥ 80 years at baseline, 277 for both, and 49 for missing covariates, leaving 6,875 participants in this analysis (Online Figure 1). Of these, 3,435 were randomized to standard BP control and 3,440 to intensive BP control. Median follow-up was 3.3 years. The mean $\pm$ standard deviation for age was 65 ± 8 years and 37% were female. Mean body mass index was 30 ± 6 kg/m², and BP was $140 \pm 16/80 \pm 11$ mm Hg. Median (interquartile range) estimated 10-year predicted ASCVD risk was 15.9% (10.7 to 23.8). Baseline characteristics by quartiles are presented in Table 1. Participants in higher quartiles were older, fewer were female, and they had lower body mass index, greater systolic BP, and lower diastolic BP.

There were 238 ASCVD events (cumulative incidence 3.5%) and 2,243 SAEs (32.6%) overall. The incidence of ASCVD events increased across quartiles of predicted risk, ranging from 1.8% in quartile 1 to 5.5% in quartile 4. The association was similar for SAEs, with 24.7% in quartile 1 and 40.5% in quartile 4. The cumulative incidence for ASCVD events was lower in the intensive arm for each quartile and the cumulative incidence for SAEs was higher in the intensive arm for each quartile (Table 2).

Each 1% higher baseline 10-year ASCVD risk score was associated with a significantly higher risk of incident ASCVD events (HR 1.04; 95% CI 1.03, 1.05) and incident SAEs (HR 1.02; 95% CI 1.02, 1.03). Harrell's C-statistic was 0.628 (95% CI 0.593 to 0.663) for ASCVD events and 0.565 (95% CI 0.553, 0.577) for SAEs. The positive association between greater hazard of incident events with higher baseline predicted 10-year risk were seen in the cubic restricted spline plots (Figure 1).

Randomization to intensive BP control was associated with a less relative hazard of ASCVD events ($p = 0.03$) and a non-significant, increased relative hazard of SAEs ($p = 0.06$) as seen in Figure 2 and Table 3. There was no evidence of effect modification of HR of ASCVD events or SAEs by group assignment and risk quartile. There was a significantly lower RD for ASCVD events with intensive BP control overall ($p = 0.03$) and a nonsignificant trend towards more SAEs with intensive BP control ($p = 0.06$). There was no evidence of effect modification of this association and RD for ASCVD events or SAEs. In the sensitivity analysis using a 10-year ASCVD risk threshold of 10%, similar magnitudes of effects were seen with intensive BP control above and below the risk threshold (Tables 2 and 3, Figure 2). There was no evidence of effect modification of the HR or RD by group assignments and threshold for either outcome.

Discussion

In this secondary analysis of participants in SPRINT without previous ASCVD, intensive BP control significantly reduced the hazard of incident ASCVD events by 25% and was associated with a nonsignificant 8% increased risk in SAEs. The net benefit was similar across the spectrum of baseline predicted 10-year ASCVD risk for both absolute and relative risk reduction.

Current hypertension guidelines recommend initiation of antihypertensive medications for primary prevention of ASCVD in adults with stage 1 hypertension and a predicted 10-year ASCVD $\geq 10\%$.⁸ For adults with predicted risk $<10\%$, there is no strong recommendation to initiate antihypertensives until stage 2 hypertension. This recommendation draws on evidence from a meta-analysis from BP trials combining primary and secondary prevention patients.⁹ This meta-analysis was published before the results of SPRINT were released. In this publication, a novel risk prediction score predicted 5-year risk of ASCVD. Participants were divided into 4 risk groups (5-year risk $<11\%$, 11% to 15%, 15 to 21%, and $>21\%$). There was similar relative risk reduction across all 4 groups but lower absolute risk reductions, and greater number needed to treat, in the lowest risk group.

Our findings extend medical knowledge. First, our analysis is the first to report a cumulative ASCVD endpoint (without HF events) in a primary prevention subgroup. These reported findings are relevant as the PCE has been validated for ASCVD events, not ASCVD events plus HF events. While we consider HF to be an important clinical event, separating out the effect of intensive BP control on ASCVD events helps isolate its specific effects for these related conditions. Second, we found the PCE to be a good discriminator for ASCVD events in the SPRINT population with a C-statistic similar to what has been found in other PCE validation studies and in validation studies of other risk-stratifying tests (e.g., C-reactive protein).^{4,3,10–12} This further supports the clinical use of PCE in selecting low- from high-risk adults in determination of primary prevention management for ASCVD. Third, we were able to directly assess the risk thresholds included in current hypertension guidelines. Fourth, a recent publication of incident harm and benefit by level of predicted ASCVD level in a primary and secondary prevention subgroup in SPRINT reached opposite conclusions from our analysis.¹³ As the PCE was not developed for use in secondary prevention, inclusion of this population likely introduced bias that shifted the measure of association for benefit away from the null. Finally, in contrast to the previous meta-analysis, we found that the benefits of intensive BP control may extend to those in the bottom quartile of ASCVD risk.

There are several reasons why our findings may have differed from those of the previous meta-analysis. First, the meta-analysis included both primary and secondary prevention cohorts. The lowest (first) and highest (fourth) risk groups included 11.2% and 70.2% adults with previous CVD events. Limiting to a primary prevention cohort would likely attenuate the overall magnitude of effect given the overall reduction in risk across these groups. Second, the risk equation in the meta-analysis was internally derived and has not been validated. Thus, it is unclear how well it predicts risk in other populations. Furthermore, the risk calculator did not include cholesterol covariates due to incomplete ascertainment in trials, reducing applicability to the PCE. Finally, the meta-analysis was largely comprised of trials of medication add-on rather than treating to a specific BP target, as was performed in SPRINT and was incorporated into recent hypertension guidelines.

Our study has limitations. It is a post hoc analysis, so the randomization design is not entirely maintained. The open-label nature of SPRINT may have introduced bias. The study duration was too short to demonstrate calibration of the PCE equation. Important segments of the population with elevated ASCVD risk and who were thus eligible for BP lowering therapy (e.g., patients with diabetes) were excluded in the original SPRINT design. SPRINT eligibility criteria required 1 CVD risk factor and age 50 years. It is unclear if adults without any CVD risk factors or younger adults may have derived benefit or harm from intensive BP control. There was no ascertainment of peripheral vascular disease or abdominal aortic aneurysm events so our ASCVD outcome did not include these endpoints. Finally, the statistical significance of both outcomes was close to 0.05, with SAEs being slightly above our predefined threshold for statistical significance. Use of lower p-value thresholds may reduce false positive findings in medical literature.¹⁴

Strengths of our analysis reflect the core design of this trial, including its use of randomization, large sample size, diverse study population, large contrast in BP, and high

follow-up rates. Second, by evaluating the ASCVD risk score in a trial setting, we can directly assess for effect modification. Third, given that nearly a quarter of participants had a baseline risk <10%, we were able to directly evaluate the threshold incorporating the recent BP guidelines. Future research should assess the role of intensive BP control in lower risk groups with long-term conditions not included in SPRINT, like stroke and diabetes. Finally, as 16.8 million United States adults meet eligibility criteria for SPRINT, we think that our findings may potentially be generalizable to many adults.¹⁵

In conclusion, in adults without baseline clinical ASCVD, the benefits of intensive BP intervention in SPRINT may extend to lower risk patients in a primary prevention subgroup. More evidence is needed to better risk stratify adults with stage 1 hypertension.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Restricted cubic spline plots and kernel density plots comparing HR for incident ASCVD events and SAEs relative to the median baseline 10-year ASCVD risk score*.

*Visualization of HR for incident ASCVD events and SAEs for the follow-up period, according to predicted 10-year ASCVD risk levels at baseline using restricted cubic spline models. The 95% confidence intervals are represented in the shaded areas. These models were expressed relative to the median 10-year ASCVD risk level, with knots specified using Harrell's method and were not prespecified.⁷ Knots were at 5.4%, 12.6%, 20.0%, and 36.9% 10-year ASCVD risk. Plots are truncated at the 0.5% and 99.5% of baseline 10-year ASCVD risk. In the following, kernel density plots show the distribution of predicted 10-year ASCVD risk levels at baseline. Dotted vertical lines indicate the 10% 10-year ASCVD risk threshold.

Figure 2. Risk difference and hazard ratio comparing intensive BP control to standard BP control for the outcomes of interest*.

*Q1–4 indicates 10-year atherosclerotic cardiovascular disease (ASCVD) risk quartiles 1 to 4, the ranges of which are denoted in Table 1. <10% and ≥10% indicates those below and above the 10% 10-year ASCVD risk threshold recommended in the clinical guidelines to guide initiation of antihypertensive medications for adults with stage 1 hypertension.⁸

Vertical lines are shown at a risk difference of 0% and a hazard ratio of 1.

Table 1

Baseline characteristics in all and by atherosclerotic cardiovascular disease (ASCVD) risk quartile

Variable	10-year ASCVD risk			
	1.1% – 10.7%	>10.7% – 15.9%	>15.9% – 23.8%	>23.8% – 61.6%
Number of participants	1,718	1,719	1,720	1,718
Intensive BP control	50%	51%	50%	49%
10-year ASCVD risk	8% (6–9)	13% (12–14)	19% (18–21)	30% (27–36)
Age (years)	59±5	63±6	67±6	73±6
Women	60%	34%	28%	27%
Black race	36%	43%	43%	21%
Body mass index (kg/m ²)	32±6	31 ±6	30±5	29±5
Systolic BP (mm Hg)	133±14	137±15	141±14	147±16
Diastolic BP (mm Hg)	81±10	81±11	80±12	78±12
Current smoker	9%	13%	18%	18%
Aspirin use	36%	42%	48%	49%
Statin use	31%	35%	38%	41%
BP medications (number)	1.7±1.1	1.8±1.1	1.8±1.0	1.8±1.0
No BP medications	14%	12%	9%	7%
Glucose (mg/dL)	98±14	99±15	99±13	99±12
Total cholesterol (mg/dL)	198± 40	195± 40	197±42	192±39
High-density lipoprotein-cholesterol (mg/dL)	51 (44–61)	50 (43–59)	50(43–60)	50 (42–61)
Triglycerides (mg/dL)	107 (78–150)	107 (77–155)	109 (78–157)	109 (79–152)

Normally-distributed continuous variables are presented as mean ± standard deviation. Non-normally distributed continuous variables are presented as median (interquartile range).

Table 2

Number of events and cumulative incidence for the primary efficacy outcome, atherosclerotic cardiovascular disease (ASCVD) events, and the primary safety outcome, serious adverse events (SAEs) in all, by baseline 10-year ASCVD risk quartile, and by a 10-year risk threshold of 10%.*

		Overall	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Risk <10%	Risk 10%	
ASCVD Events	Standard	Events/All	135/3,435	21/849	22/850	40/860	52/876	19/746	116/2,689
		Incidence	3.9%	2.5%	2.6%	4.7%	5.9%	2.5%	4.3%
	Intensive	Events/All	103/3,440	10/869	22/869	28/860	43/842	10/757	93/2,683
		Incidence	3.0%	1.2%	2.5%	3.3%	5.1%	1.3%	3.5%
SAEs	Standard	Events/All	1084/3,435	202/849	253/850	276/860	353/876	173/746	911/2,689
		Incidence	31.6%	23.8%	29.8%	32.1%	40.3%	23.2%	33.9%
	Intensive	Events/All	1159/3,440	222/869	284/869	310/860	343/842	191/757	968/2,683
		Incidence	33.7%	25.5%	32.7%	36.0%	40.7%	25.2%	36.1%

* Presented as number of events/number of participants and cumulative incidence. Quartile definitions can be found in Table 1. Risk < and 10% refers to a 10-year ASCVD risk threshold of 10%.

Table 3

Hazard ratios, risk differences, and 95% confidence intervals comparing intensive to standard therapy for atherosclerotic cardiovascular disease (ASCVD) events and serious adverse events (SAEs), number of events, and cumulative incidence of events in all and by baseline 10-year ASCVD risk quartile *

	Overall	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value	Risk <10%	Risk >10%	P-value
ASCVD Events									
Hazard ratio	0.75 (0.58, 0.97)	0.45 (0.21, 0.95)	1.00 (0.56, 1.81)	0.70 (0.43, 1.13)	0.84 (0.56, 1.26)	0.39	0.50 (0.24, 1.09)	0.79 (0.60, 1.04)	0.29
Risk Difference	-0.94 (-1.8, -0.1)	-1.3 (-2.6, -0.1)	0.0 (-1.5, 1.4)	-1.4 (-3.2, -0.4)	-0.8 (-3.0, 1.3)	0.84	-1.2 (-2.6, 0.2)	-0.8 (-1.9, 0.2)	0.67
SAEs									
Hazard ratio	1.08 (1.00, 1.17)	1.06 (0.88, 1.29)	1.14 (0.96, 1.35)	1.15 (0.97, 1.35)	1.01 (0.87, 1.17)	0.57	1.09 (0.89, 1.35)	1.08 (0.99, 1.18)	0.90
Risk Difference	2.1 (-0.1, 4.4)	1.8 (-2.3, 5.8)	2.9 (-1.5, 7.3)	4.0 (-0.5, 8.4)	0.4 (-4.2, 5.1)	0.82	2.0 (-2.3, 6.4)	2.2 (-0.3, 4.8)	0.95

* Quartile definitions can be found in Table 1. Risk < and 10% refers to a 10-year ASCVD risk threshold of 10%. The P-value for effect modification assesses the interaction of quartile or threshold of baseline risk with group assignment.