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Impact of Cardiovascular Risk on the Relative Benefit and Harm of Intensive Treatment of Hypertension

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ABSTRACT

BACKGROUND The lower rate of primary outcome events in the intensive treatment group in SPRINT (Systolic Pressure Intervention Trial) was associated with increased clinically significant serious adverse events (SAEs). In 2017, the American College of Cardiology/American Heart Association issued risk-based blood pressure treatment guidelines. The authors hypothesized that stratification of the SPRINT population by degree of future cardiovascular disease (CVD) risk might identify a group which could benefit the most from intensive treatment.

OBJECTIVES This study investigated the effect of baseline 10-year CVD risk on primary outcome events and all-cause SAEs in SPRINT.

METHODS Stratifying by quartiles of baseline 10-year CVD risk, Cox proportional hazards models were used to examine the associations of treatment group with the primary outcome events and SAEs. Using multiplicative Poisson regression, a predictive model was developed to determine the benefit-to-harm ratio as a function of CVD risk.

RESULTS Within each quartile, there was a lower rate of primary outcome events and no significant differences in all-cause SAEs for the intensive treatment group compared to the standard treatment group. From the first to fourth quartiles, the number needed to treat to prevent primary outcomes decreased from 91 to 38. The number needed to harm for all-cause SAEs increased from 62 to 250. The predictive model demonstrated significantly increasing benefit-to-harm ratios (± SE) of 0.50 ± 0.15, 0.78 ± 0.26, 2.13 ± 0.73, and 4.80 ± 1.86, for the first, second, third, and fourth quartile, respectively (p for trend <0.001). All possible pairwise comparisons of between-quartile mean values of benefit-to-harm ratios were significantly different ($p < 0.001$).

CONCLUSIONS In SPRINT, those with lower baseline CVD risk had more harm than benefit from intensive treatment, whereas those with higher risk had more benefit. With the 2017 American College of Cardiology/American Heart Association blood pressure treatment guidelines, this analysis may help providers and patients make decisions regarding the intensity of blood pressure treatment. (J Am Coll Cardiol 2018;71:1601–10) © 2018 by the American College of Cardiology Foundation.

The SPRINT (Systolic Pressure Intervention Trial) tested the hypothesis that treatment to a systolic blood pressure (SBP) goal <120 mm Hg (intensive treatment) in patients ≥50 years of age at high risk for cardiovascular events (without diabetes) was superior to an SBP treatment goal <140 mm Hg (standard treatment) (1). The primary outcome was a composite of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute compensated heart failure, or death from cardiovascular causes. Over the 3.26 years of follow-up, those randomized to the intensive-treatment arm had a mean achieved SBP of 121.5 mm Hg, whereas those in the standard-treatment arm had a mean achieved SBP of 134.6 mm Hg (1). Compared to those in the standard-treatment arm, those in the intensive-treatment arm had a 25% lower incidence of the primary outcome events ($p < 0.001$) and a 27% reduction in all-cause mortality ($p = 0.003$) (1). The number needed to treat (NNT) was 61 to prevent 1 primary cardiovascular outcome and was 90 to prevent 1 death (1). The intensive treatment was equally effective in those who were 75 years of age or older (2).

Largely based on the results of SPRINT, the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (hereafter referred to as the 2017 ACC/AHA blood pressure guidelines) has recommended intensive treatment in SPRINT-eligible patients (3). If this recommendation is implemented in

SPRINT-eligible adults, it is estimated that 107,500 deaths could be averted annually in the United States (4). The majority of averted deaths, 67,300 per year, would occur in those ≥75 years of age because of the high event rate in this group. Intensive treatment is projected to prevent 32,700 deaths annually among those with chronic kidney disease and to prevent 46,100 cases of heart failure (4). The downside of intensive compared with standard treatment is an additional 56,100 episodes of hypotension, 34,400 episodes of syncope, 43,400 episodes of electrolyte abnormalities, and 88,700 cases of acute renal injury or acute renal failure (4).

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Clinicians and patients are therefore faced with a dilemma. Although there is significant reduction in cardiovascular events and death from intensive treatment, it may be accompanied by additional, clinically significant serious adverse events (SAEs). While the 2017 ACC/AHA blood pressure guidelines recommend intensive treatment for all SPRINT-eligible patients, strategies to identify those who might achieve greater benefit than harm from intensive treatment might be useful. Using probability of the risk for a future cardiovascular event to guide blood pressure management is an emerging paradigm (3). We hypothesized that stratification of the SPRINT population by degree of future cardiovascular disease (CVD) risk might identify a group who could benefit the most from intensive treatment, with the least amount of harm from SAEs.

METHODS

DATA ACQUISITION AND HUMAN SUBJECTS. We obtained the SPRINT database through a data use agreement with the *New England Journal of Medicine*, as part of their SPRINT Data Analysis Challenge (5). As an analysis of existing and de-identified data, the Bridgeport Hospital Internal Review Board (Yale New Haven Health) and the Houston Methodist Research Institute Internal Review Board exempted the study from approval.

STATISTICAL ANALYSIS. Subject-specific estimates of the 10-year ACC/AHA CVD risk were determined using the risk prediction equations from the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (6). The SPRINT population was then stratified into quartiles based on 10-year CVD risk. Baseline demographics, risk factors, and achieved SBP between standard and intensive treatment were calculated as mean ± SD for continuous variables and number (percentage) for categorical variables. Tests for trend across quartiles of 10-year CVD risk were conducted by modeling the quartiles as a continuous variable in linear regression models for continuous variables and the Cochran-Armitage test for trend for categorical variables. Cox proportional hazards regression was used to determine treatment hazard ratios for SPRINT primary outcome events, all-cause mortality, and SAEs within each risk quartile. The proportionality assumption of the Cox model was assessed, and there was no evidence for the violation of this assumption. A sensitivity analysis was also performed for this risk stratification after removing those patients with clinical or subclinical CVD. We calculated the following parameters: relative risk reduction, absolute risk reduction, NNT, absolute SAE risk increase, and number needed to harm (NNH).

Following the original design of SPRINT, SAEs were defined as events that were fatal or life-threatening, resulted in disability, led to or prolonged hospitalization, or were judged by investigators to represent a significant hazard or harm to the individual (1). Conditions of interest included hypotension, syncope, bradycardia, electrolyte abnormalities, injurious falls, and acute kidney injury or acute renal failure.

PREDICTIVE MODEL. A predictive model was developed to determine the benefit-to-harm ratio as a function of 10-year CVD risk quartile for SPRINT participants. In this model, we used all-cause SAEs as a robust measure of harm. To develop this predictive model, we employed multiplicative Poisson regression (7) to obtain the average quartile-specific number of predicted events from 4 models: standard treatment using primary outcome events and person-days; standard treatment using all-cause SAEs and SAE-days; intensive treatment using primary outcome events and person-days; and intensive treatment using all-cause SAEs and SAE-days. The analysis accounted for the first primary outcome and the first SAE experienced by a participant; recurrent events were not part of the analysis. Therefore, days were calculated as total days from enrollment to the first primary outcome event or SAE, dropping out, or study end, whichever occurred first. Each model employed sum-to-zero constraints via use of dummy indicator variables for the 4 quartiles, without use of a constant term. For each of the 4 models, the predicted probability of a primary outcome event and predicted probability of a SAE were determined for each subject. Quartile-specific benefit-to-harm was

ABBREVIATIONS AND ACRONYMS

AAFP = American Academy of Family Physicians

ACC = American College of Cardiology

ACP = American College of Physicians

AHA = American Heart Association

CVD = cardiovascular disease

JNC8 = Eighth Joint National Committee

NNH = number needed to harm

NNT = number needed to treat

SAE = serious adverse event

SBP = systolic blood pressure

TABLE 1 Study Demographics by Quartile of 10-Year CVD Risk, by SPRINT Treatment Arm

	1st Quartile (<11.5%)			2nd Quartile (11.5%–18.1%)		
	Intensive (n = 1,178)	Standard (n = 1,153)	p Value	Intensive (n = 1,152)	Standard (n = 1,179)	p Value
Age*	59.2 ± 5.1	59.1 ± 5.2	NS	64.1 ± 6.0	63.8 ± 5.9	NS
75 yrs of age or older	4 (0.4)	1 (0.1)	NS	27 (2.3)	35 (3.0)	NS
Female*	665 (56.5)	631 (54.7)	NS	372 (32.3)	354 (30.0)	NS
Race/ethnic group*						
Non-Hispanic black	388 (32.9)	391 (33.9)	NS	478 (41.5)	467 (39.6)	NS
Hispanic	212 (18.0)	195 (16.9)		98 (8.5)	123 (10.4)	
Non-Hispanic white	548 (46.5)	549 (47.6)		564 (49.0)	570 (48.4)	
Other	30 (2.6)	18 (1.6)		12 (1.0)	19 (1.6)	
Black race	434 (36.8)	424 (36.8)	NS	487 (42.3)	486 (41.2)	NS
Chronic kidney disease	241 (20.5)	231 (20.0)	NS	259 (22.5)	245 (20.8)	NS
Cardiovascular disease	191 (16.2)	203 (17.6)	NS	183 (15.9)	218 (18.5)	NS
Clinical	142 (12.1)	152 (13.2)	NS	140 (12.2)	178 (15.1)	0.040
Subclinical	67 (5.7)	69 (6.0)	NS	59 (5.1)	61 (5.2)	NS
Baseline blood pressure, mm Hg*						
Systolic	133.1 ± 14.3	133.1 ± 14.0	NS	137.8 ± 14.9	138.1 ± 14.1	NS
Diastolic	80.5 ± 10.8	80.1 ± 10.8	NS	80.1 ± 11.4	80.6 ± 11.6	NS
Serum creatinine, mg/dl	1.0 ± 0.3	1.0 ± 0.3	NS	1.1 ± 0.3	1.1 ± 0.3	NS
Estimated GFR, ml/min/1.73 m^2						
Among all participants	76.2 ± 21.1	76.5 ± 21.1	NS	75.1 ± 20.6	74.8 ± 20.0	NS
Among those with estimated GFR ≥60 ml/min/1.73 m^2	83.8 ± 16.0	83.8 ± 16.2	NS	82.9 ± 15.9	81.8 ± 15.7	NS
Among those with estimated GFR <60 ml/min/1.73 m^2	46.9 ± 10.3	47.4 ± 10.5	NS	48.3 ± 9.6	48.3 ± 9.7	NS
Ratio of urinary albumin (mg) to creatinine (g)	28.9 ± 105.3	38.3 ± 193.6	NS	36.6 ± 170.1	29.8 ± 90.9	NS
Fasting total cholesterol, mg/dl*	195.1 ± 42.2	193.7 ± 41.6	NS	192.4 ± 41.2	191.5 ± 40.2	NS
Fasting HDL cholesterol, mg/dl*	53.4 ± 14.7	53.9 ± 14.8	NS	52.3 ± 13.4	51.4 ± 14.1	NS
Fasting total triglycerides, mg/dl	125.0 ± 68.4	123.1 ± 76.1	NS	126.4 ± 106.9	135.5 ± 125.5	NS
Fasting plasma glucose, mg/dl*	98.8 ± 15.5	98.4 ± 14.2	NS	99.1 ± 14.0	99.6 ± 14.8	NS
Statin use	419 (35.7)	436 (38.2)	NS	451 (39.4)	498 (42.4)	NS
Aspirin use	490 (41.7)	484 (42.0)	NS	574 (49.9)	571 (48.5)	NS
Smoking status*						
Never smoked	643 (54.6)	627 (54.4)	NS	486 (42.2)	504 (42.8)	NS
Former smoker	416 (35.3)	425 (36.9)		497 (43.1)	505 (42.8)	
Current smoker	118 (10.0)	101 (8.8)		169 (14.7)	167 (14.2)	
Missing data	1 (0.1)	0 (0)		0 (0)	3 (0.3)	
Body mass index, kg/m^2	31.7 ± 6.4	31.7 ± 6.5	NS	30.4 ± 5.8	30.6 ± 5.5	NS
Antihypertensive agents per participant	1.7 ± 1.1	1.8 ± 1.1	NS	1.9 ± 1.1	1.8 ± 1.1	0.048
Not using antihypertensive agents*	165 (14.0)	135 (11.7)	NS	114 (9.9)	143 (12.1)	NS

Values are mean ± SD or n (%). *Components of the 10-yr CVD risk algorithm.
ACC = American College of Cardiology; AHA = American Heart Association; CVD = cardiovascular disease; GFR = glomerular filtration rate; HDL = high-density lipoprotein.

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then based on the ratio of the difference of average predicted primary outcome events in the standard and intensive treatments to the difference of predicted SAEs in standard and intensive treatment, using the standard deviation in quadrature sum for error determination. To determine if the benefit-to-harm ratios were significantly different between quartiles, within each quartile we simulated 1,000 random variates of the benefit-to-harm ratio using the mean ± SD. One-way analysis of variance was then run with Scheffe multiple comparison tests to determine the significance of all possible pairwise comparisons of between-quartile mean values of benefit-to-harm ratios.

Statistical analyses were performed with STATA version 15 (STATA Corp., College Station, Texas). All p values were 2-tailed, and p values <0.05 were considered statistically significant.

TABLE 1 Continued

3rd Quartile (18.2%–28.9%)			4th Quartile (>28.9%)			p Value for Quartile Trend
Intensive (n = 1,172)	Standard (n = 1,159)	p Value	Intensive (n = 1,160)	Standard (n = 1,170)	p Value	
69.5 ± 6.7	69.7 ± 6.8	NS	78.9 ± 5.7	78.9 ± 5.9	NS	<0.001
210 (18.1)	196 (16.7)	NS	934 (79.8)	936 (80.7)	NS	<0.001
308 (26.3)	319 (27.5)	NS	325 (28.0)	333 (28.5)	NS	<0.001
387 (33.0)	438 (37.8)	0.007	118 (10.2)	118 (10.1)	NS	<0.001
103 (8.8)	81 (7.0)		87 (7.5)	79 (6.8)		<0.001
649 (55.4)	624 (53.8)		932 (80.3)	950 (81.2)		<0.001
33 (2.8)	16 (1.4)		23 (2.0)	23 (2.0)		NS
398 (34.0)	451 (38.9)	0.014	127 (11.0)	123 (10.5)	NS	<0.001
322 (27.5)	318 (27.4)	NS	508 (43.8)	521 (44.5)	NS	<0.001
246 (21.0)	219 (18.9)	NS	319 (27.5)	290 (24.8)	NS	<0.001
204 (17.4)	188 (16.2)	NS	292 (25.2)	259 (22.1)	NS	<0.001
66 (5.6)	55 (4.8)	NS	55 (4.7)	58 (5.0)	NS	NS
141.2 ± 15.0	141.1 ± 14.7	NS	146.6 ± 15.7	146.3 ± 15.8	NS	<0.001
78.3 ± 12.0	78.1 ± 12.3	NS	74.0 ± 12.3	73.4 ± 11.9	NS	<0.001
1.1 ± 0.3	1.1 ± 0.3	NS	1.1 ± 0.4	1.1 ± 0.3	NS	<0.001
72.0 ± 20.3	72.3 ± 20.0	NS	63.6 ± 18.0	63.3 ± 18.5	NS	<0.001
80.9 ± 15.8	81.3 ± 15.0	NS	76.2 ± 12.4	76.1 ± 13.5	NS	<0.001
48.6 ± 9.2	48.6 ± 9.3	NS	47.6 ± 9.1	47.4 ± 9.1	NS	NS
40.3 ± 128.9	37.5 ± 125.3	NS	70.4 ± 264.6	58.7 ± 179.9	NS	<0.001
190.1 ± 40.8	191.3 ± 42.3	NS	183.2 ± 40.6	183.8 ± 39.1	NS	<0.001
52.3 ± 13.7	52.8 ± 14.7	NS	53.8 ± 15.5	53.2 ± 14.7	NS	NS
129.3 ± 93.1	127.9 ± 90.9	NS	118.4 ± 68.5	121.7 ± 78.0	NS	NS
99.1 ± 12.8	98.9 ± 12.7	NS	98.3 ± 12.5	98.3 ± 11.6	NS	NS
534 (45.9)	562 (48.8)	NS	574 (49.9)	572 (49.4)	NS	<0.001
628 (53.8)	627 (54.3)	NS	712 (61.5)	661 (56.5)	0.015	<0.001
427 (36.4)	443 (38.2)	NS	490 (42.2)	491 (42.0)	NS	<0.001
507 (43.3)	486 (41.9)		553 (47.7)	574 (49.1)		<0.001
235 (20.1)	228 (19.7)		116 (10.0)	104 (8.9)		NS
3 (0.3)	2 (0.2)		1 (0.1)	1 (0.1)		NS
29.6 ± 5.2	29.0 ± 5.1	0.006	27.8 ± 5.0	27.8 ± 4.8	NS	<0.001
1.9 ± 1.0	1.9 ± 1.0	NS	1.9 ± 1.0	1.9 ± 1.0	NS	<0.001
84 (7.2)	83 (7.2)	NS	68 (5.9)	88 (7.5)	NS	<0.001

RESULTS

PATIENTS. Consistent with the entry criteria of SPRINT, this was a high-risk group; one-half of the population had a 10-year risk of a cardiovascular event of ≥18.2% (Table 1). There was no significant difference in baseline SBP between intensive treatment and standard treatment within each of the 10-year CVD risk quartiles (Table 1). There was a significant trend of increasing baseline SBP (p for trend <0.001) and clinical cardiovascular disease (p for trend <0.001) with increasing quartile of 10-year CVD risk. For both the intensive and standard groups, there was no interquartile difference in achieved SBP.

There were significant baseline demographic differences between each quartile (Table 1); many of these differences were accounted for by components of the risk score calculations, such as age and baseline blood pressure. Of note, estimated glomerular filtration rate (p for trend <0.001), total cholesterol levels (p for trend <0.001), body mass index (p for trend <0.001), and not using antihypertensive agents (p for trend <0.001) were lower in the higher-risk groups. Ratio of urinary albumin (mg) to

TABLE 2 Primary Outcome Events and All-Cause Mortality Events, Hazard Ratio, Absolute Risk Reduction, and NNT by 10-Year CVD Risk Quartile

	Intensive	Standard	Hazard Ratio (95% CI)	Absolute Risk Reduction (95% CI)	NNT
Primary outcome events					
1st quartile (<11.5%)	33/1,178 (2.8)	45/1,153 (3.9)	0.64 (0.41 to 1.02)	1.1 (−0.4 to 2.6)	91
2nd quartile (11.5%-18.1%)	44/1,152 (3.8)	59/1,179 (5.0)	0.75 (0.51 to 1.12)	1.2 (−0.5 to 2.9)	83
3rd quartile (18.2%-28.9%)	64/1,172 (5.5)	81/1,159 (7.0)	0.78 (0.56 to 1.10)	1.5 (−0.4 to 3.5)	67
4th quartile (>28.9%)	102/1,160 (8.8)	133/1,170 (11.4)	0.73 (0.56 to 0.95)	2.6 (0.1 to 5.0)	38
All-cause mortality					
1st quartile (<11.5%)	19/1,178 (1.6)	22/1,153 (1.9)	0.81 (0.43 to 1.50)	0.3 (−0.8 to 1.4)	333
2nd quartile (11.5%-18.1%)	26/1,152 (2.3)	36/1,179 (3.1)	0.79 (0.47 to 1.33)	0.8 (−0.5 to 2.1)	125
3rd quartile (18.2%-28.9%)	35/1,172 (3.0)	50/1,159 (4.3)	0.71 (0.46 to 1.10)	1.3 (−0.2 to 2.9)	77
4th quartile (>28.9%)	74/1,160 (6.4)	101/1,170 (8.6)	0.75 (0.55 to 1.03)	2.2 (0.1 to 4.4)	45

Values are n/N (%), unless otherwise indicated.
CI = confidence interval; NNT = number needed to treat.

TABLE 3 Serious Adverse Events, Hazard Ratio, Absolute Risk Reduction, and NNH by 10-Year CVD Risk Quartile

	Intensive	Standard	Hazard Ratio (95% CI)	Absolute SAE Risk Increase (95% CI)	NNH
All-cause serious adverse events					
1st quartile (<11.5%)	337/1,178 (28.6)	311/1,153 (27.0)	1.1 (0.9 to 1.2)	1.6 (−2.0 to 5.3)	62
2nd quartile (11.5-18.1%)	412/1,152 (35.8)	396/1,179 (33.6)	1.1 (1.0 to 1.3)	2.2 (−1.7 to 6.0)	45
3rd quartile (18.2%-28.9%)	458/1,172 (39.1)	444/1,159 (38.3)	1.0 (0.9 to 1.2)	0.8 (−3.2 to 4.7)	125
4th quartile (>28.9%)	582/1,160 (50.2)	582/1,170 (49.7)	1.0 (0.9 to 1.1)	0.4 (−3.6 to 4.5)	250
Hypotension					
1st quartile (<11.5%)	16/1,178 (1.4)	11/1,153 (1.0)	1.4 (0.6 to 3.0)	0.4 (−0.5 to 1.3)	250
2nd quartile (11.5%-18.1%)	20/1,152 (1.7)	15/1,179 (1.3)	1.4 (0.7 to 2.7)	0.5 (−0.5 to 1.5)	200
3rd quartile (18.2%-28.9%)	34/1,172 (2.9)	21/1,159 (1.8)	1.6 (0.9 to 2.8)	1.1 (−0.1 to 2.3)	91
4th quartile (>28.9%)	40/1,160 (3.4)	19/1,170 (1.6)	2.1 (1.2 to 3.7)	1.8 (0.5 to 3.1)	55
Syncope					
1st quartile (<11.5%)	15/1,178 (1.3)	8/1,153 (0.7)	1.8 (0.8 to 4.2)	0.6 (−0.2 to 1.4)	167
2nd quartile (11.5%-18.1%)	22/1,152 (1.9)	13/1,179 (1.1)	1.8 (0.9 to 3.5)	0.8 (−0.2 to 1.8)	125
3rd quartile (18.2%-28.9%)	27/1,172 (2.3)	26/1,159 (2.2)	1.0 (0.6 to 1.8)	0.1 (−1.1 to 1.3)	1,000
4th quartile (>28.9%)	42/1,160 (3.6)	33/1,170 (2.8)	1.3 (0.8 to 2.0)	0.8 (−0.6 to 2.2)	125
Bradycardia					
1st quartile (<11.5%)	6/1,178 (0.5)	5/1,153 (0.4)	1.1 (0.3 to 3.7)	0.1 (−0.5 to 0.6)	1,000
2nd quartile (11.5%-18.1%)	26/1,152 (2.3)	13/1,179 (1.1)	2.1 (1.1 to 4.1)	1.2 (0.1 to 2.2)	83
3rd quartile (18.2%-28.9%)	14/1,172 (1.2)	16/1,159 (1.4)	0.9 (0.4 to 1.8)	−0.2 (−1.1 to 0.7)	−500
4th quartile (>28.9%)	41/1,160 (3.5)	39/1,170 (3.3)	1.1 (0.7 to 1.6)	0.2 (−1.3 to 1.7)	500
Electrolyte abnormality					
1st quartile (<11.5%)	31/1,178 (2.6)	18/1,153 (1.6)	1.7 (0.9 to 3.0)	1.1 (−0.1 to 2.2)	91
2nd quartile (11.5%-18.1%)	24/1,152 (2.1)	23/1,179 (2.0)	1.1 (0.6 to 1.9)	0.1 (−1.0 to 1.2)	1,000
3rd quartile (18.2%-28.9%)	33/1,172 (2.8)	28/1,159 (2.4)	1.2 (0.7 to 1.9)	0.4 (−0.9 to 1.7)	250
4th quartile (>28.9%)	56/1,160 (4.8)	38/1,170 (3.2)	1.5 (1.0 to 2.2)	1.6 (0.0 to 3.2)	62
Injurious falls					
1st quartile (<11.5%)	12/1,178 (1.0)	8/1,153 (0.7)	1.4 (0.6 to 3.5)	0.3 (−0.4 to 1.1)	333
2nd quartile (11.5%-18.1%)	8/1,152 (0.7)	13/1,179 (1.1)	0.6 (0.3 to 1.5)	−0.4 (−1.1 to 0.4)	−250
3rd quartile (18.2%-28.9%)	24/1,172 (2.0)	18/1,159 (1.6)	1.3 (0.7 to 2.4)	0.5 (−0.6 to 1.6)	200
4th quartile (>28.9%)	61/1,160 (5.3)	71/1,170 (6.1)	0.9 (0.6 to 1.2)	−0.8 (−2.7 to 1.1)	−125
Acute kidney injury or acute renal failure					
1st quartile (<11.5%)	25/1,178 (2.1)	21/1,153 (1.8)	1.1 (0.6 to 2.0)	0.3 (−0.8 to 1.4)	333
2nd quartile (11.5%-18.1%)	38/1,152 (3.3)	19/1,179 (1.6)	2.1 (1.2 to 3.7)	1.7 (0.4 to 2.9)	59
3rd quartile (18.2%-28.9%)	56/1,172 (4.8)	27/1,159 (2.3)	2.1 (1.3 to 3.3)	2.4 (0.9 to 3.9)	42
4th quartile (>28.9%)	74/1,160 (6.4)	50/1,170 (4.3)	1.5 (1.1 to 2.1)	2.1 (0.3 to 3.9)	48

Values are n/N (%), unless otherwise indicated.
CI = confidence interval; NNH = number needed to harm; SAE = serious adverse event.

creatinine (g) (p for trend <0.001) and number of antihypertensive agents per patient (p for trend <0.001) were higher in the higher-risk groups.

There were 2,343 patients 75 years of age or older. Among this group, 406 (17.3%) were in the third quartile of baseline CVD risk, and 1,870 (79.8%) were in the fourth quartile. Hence, only 2.9% of those 75 years of age or older had 10-year CVD risk <18.2%.

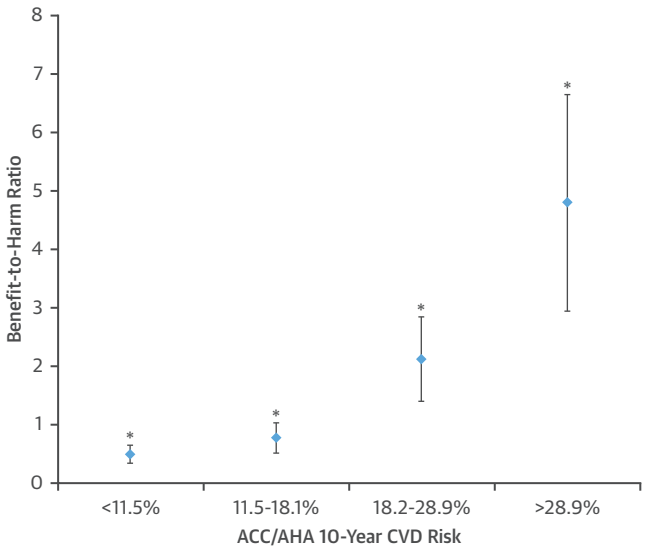
PRIMARY OUTCOMES AND MORTALITY. From the first to the fourth quartile, primary outcome events and all-cause mortality increased for both the intensive and standard treatment groups (p for trend <0.001) (Table 2). Hazard ratios for primary outcome events and all-cause mortality favored the intensive treatment group in all quartiles (Table 2). Absolute risk reduction increased from the first to the fourth quartile (Table 2). A sensitivity analysis that removed those with clinical or subclinical CVD did not alter these results. Because the absolute risk reduction increased, the NNT progressively decreased for the primary outcome events and all-cause mortality from the first to the fourth quartile (Table 2).

SERIOUS ADVERSE EVENTS. From the first to the fourth quartile, there was a significant increase in all-cause SAEs for both the intensive and standard treatment groups (p for trend <0.001) (Table 3). There was no significant difference between standard and intensive treatment within each quartile for all-cause SAEs (Table 3). However, the absolute difference in all-cause SAEs between the treatment groups decreased in the third and fourth quartile (Table 3). Hence, the NNH for all-cause SAEs increased from 62 in the first quartile to 250 in the fourth quartile (Table 3).

Within quartiles, there was no significant difference between standard and intensive treatment for syncope, injurious falls, and electrolyte abnormality (Table 3). There was significantly more hypotension in the intensive group in the fourth quartile ($p < 0.01$); more acute kidney injury/acute renal failure in the intensive group in the second, third, and fourth quartiles ($p < 0.05$); and more bradycardia in the intensive group in the second quartile ($p < 0.05$) (Table 3).

PREDICTIVE MODEL. The output of the predictive model of benefit-to-harm ratio of intensive treatment as a function of the 10-year CVD risk quartile demonstrated significantly increasing ratios (± SE) of 0.50 ± 0.15, 0.78 ± 0.26, 2.13 ± 0.73, and 4.80 ± 1.86, for the first, second, third, and fourth quartiles, respectively (p for trend <0.001) (Figure 1). All possible pairwise comparisons of between-quartile mean values of benefit-to-harm ratios were significantly different ($p < 0.001$). With a benefit-to-harm ratio <1.00, the results suggest that those in the first and second quartiles have greater harm than benefit from intensive treatment. By contrast, with a benefit-to-harm ratio >1.00, those in the third and fourth quartiles have greater benefit than harm from intensive treatment.

FIGURE 1 Benefit-to-Harm Ratios of Intensive Treatment by 10-Year CVD Risk Quartile

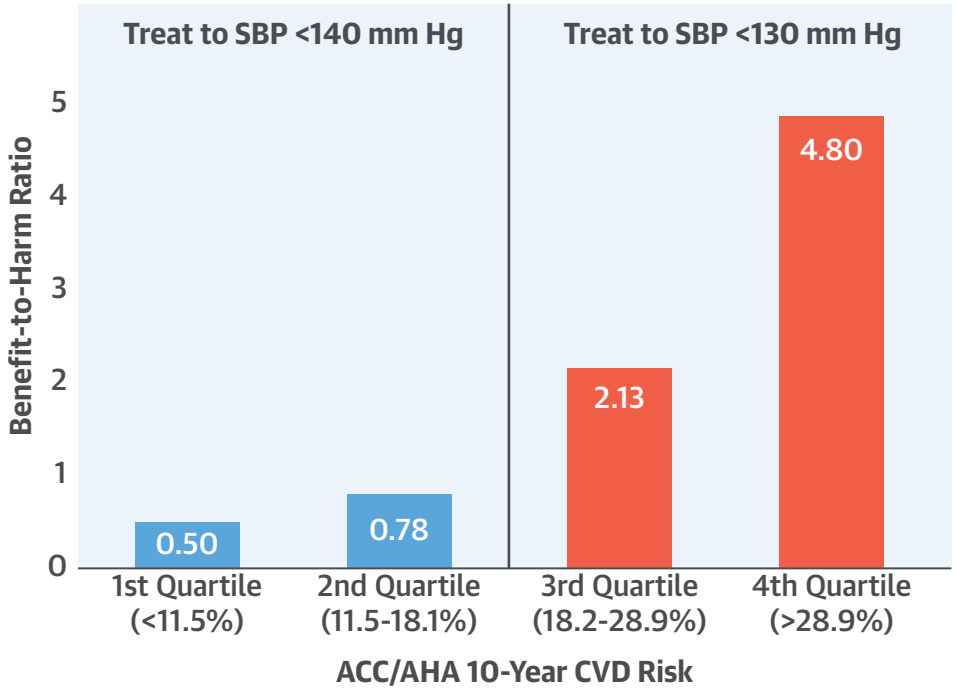


Benefit-to-harm ratios (± SE) of intensive treatment by quartile of CVD risk are shown. All possible pairwise comparisons of between-quartile mean values of benefit-to-harm ratios were significantly different (*$p < 0.001$). ACC = American College of Cardiology; AHA = American Heart Association; CVD = cardiovascular disease.

DISCUSSION

SPRINT examined the effect of intensive treatment to an SBP <120 mm Hg compared with a standard treatment goal of <140 mm Hg in patients ≥50 years of age who were at high risk for cardiovascular events. This current analysis suggests that when the SPRINT participants are stratified by the commonly used ACC/AHA CVD risk estimate, a group can be identified that had more harm than benefit from intensive treatment, and conversely, a group can be identified that had more benefit than harm (Central Illustration). Specifically, these results suggest that in those SPRINT participants with lower 10-year risk of a future cardiovascular event (<18.2%), harm of intensive treatment outweighed the benefits. However, for those with a 10-year risk ≥18.2%, benefit of intensive treatment outweighed the harm. The 2017 ACC/AHA blood pressure guidelines recommend an intensive SBP target of <130 mm Hg for hypertensive

CENTRAL ILLUSTRATION **Treatment Recommendations Based on Benefit and Harm Experienced in SPRINT by 10-Year CVD Risk**



Phillips, R.A. et al. J Am Coll Cardiol. 2018;71(15):1601-10.

With a benefit-to-harm ratio <1.00, the results suggest that for those in the first and second quartiles (<18.2%), intensive treatment would lead to greater harm of SAEs than benefit of reduced primary outcome events. By contrast, with a benefit-to-harm ratio >1.00, those in the third and fourth quartiles (≥18.2%) have greater benefit than harm from intensive treatment. While the 2017 ACC/AHA blood pressure guidelines recommend an intensive target SBP of <130 mm Hg for hypertensive patients with 10-year ACC/AHA CVD risk >10%, the results of the present analysis of SPRINT suggest a SBP target of <130 mm Hg would be appropriate for hypertensive individuals with 10-year CVD risk ≥18.2%. ACC = American College of Cardiology; AHA = American Heart Association; CVD = cardiovascular disease; SBP = systolic blood pressure.

individuals with 10-year ACC/AHA CVD risk ≥10%; however, the current analysis of SPRINT suggests an intensive SBP target for hypertensive individuals with 10-year CVD risk ≥18.2% (**Central Illustration**).

Based on historical response to the release of blood pressure guidelines, it is likely that considerable controversy will be generated by the recommendation from the 2017 ACC/AHA blood pressure guidelines for intensive blood pressure lowering. This is due to a combination of limited trial data supporting an intensive SBP goal, reluctance to aggressively treat elderly patients, and the likelihood that office blood pressure measurement obtained in the real-world clinical setting will most likely be 10 mm Hg higher than those obtained in the clinical trial setting such as SPRINT (8). Until SPRINT, there was virtually no trial-based evidence to support an intensive blood pressure goal <120/80 mm Hg in patients ≥60 years of age without diabetes. Prior to SPRINT, no trial in this group had achieved an average SBP <143 mm Hg (9,10). Furthermore, even those individuals in these trials who achieved an SBP <140 mm Hg did not show incremental benefit. For example, in the SHEP (Systolic Hypertension in the Elderly Program) trial, where the entry criteria included SBP >170 mm Hg, those who achieved an SBP <160 mm Hg had a 33% reduction in stroke, with a further 5% reduction accrued to those with SBP <150 mm Hg (11). However, there was no further reduction in events seen in those who achieved a SBP <140 mm Hg.

As a result, in 2014, prior to the SPRINT results, the 2014 Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC8)

recommended a goal of <140/90 mm Hg in those <60 years of age and a more relaxed goal of <150/90 mm Hg in those ≥60 years of age (hereafter referred to as JNC8 panel member report) (12). Almost simultaneously with the publication of the JNC8 guidelines, a minority subgroup of the guidelines committee published a critique of the JNC8 recommendations (13). Although they agreed there was no hard outcome-based evidence (i.e., stroke, CVD, or mortality) to support a blood pressure goal <140/90 mm Hg in those 60 years of age or older, they argued that relaxation of the guidelines would lead to undertreatment of those groups who are at high risk for complications of hypertension, particularly African Americans. This position was supported by the Association of Black Cardiologists' Board of Directors, who also argued that since no harm could be proven by lowering blood pressure to <140/90 mm Hg in those 60 years of age or older, it was imprudent to raise the target to <150/90 mm Hg (14).

Because SPRINT is the only trial that supports intensive SBP reduction to a goal <120 mm Hg in older adults without diabetes, a recent systematic review suggested that there is only low- to moderate-strength evidence that a target of <140/85 mm Hg is beneficial in this age group (15). Based on this, the American College of Physicians (ACP)/American Academy of Family Physicians (AAFP) recommended a SBP goal of <150 mm Hg for adults 60 years of age or older (hereafter referred to as the 2017 ACP/AAFP blood pressure guideline) and only gave a grade of "weak recommendation, low-quality evidence" for an SBP goal <140 mm Hg in those 60 years of age or older at high cardiovascular risk (16). Despite the finding that SPRINT results were equally efficacious in those 75 years of age or older, because of concerns about side effects, some post-SPRINT expert opinion suggests a SBP goal <140 mm Hg in this older age group (2,17). In our analysis, 97.1% of those 75 years of age or older had 10-year CVD risk ≥18.2%, suggesting that nearly all patients in this age group would benefit from intensive treatment.

Blood pressure in SPRINT was measured with an automatic oscillometric monitor that was programmed to take 3 consecutive seated blood pressures after 5 min of sitting, an approach that generally yields an SBP that is 7 to 10 mm Hg lower than a typical office blood pressure (18). Therefore, it has been suggested that when SPRINT results are translated from the clinical trial to everyday practice, an office SBP goal <120 mm Hg would be too aggressive, and an office SBP <130 mm Hg would represent a "real-life" intensive blood pressure goal (8). Indeed, this is the position of the 2017 ACC/AHA blood pressure guidelines, which recognizes that the intensive treatment to an SBP <120 mm Hg measured in the SPRINT trial is equivalent to a clinical practice-intensive treatment to an SBP <130 mm Hg (3).

Given the conflicting blood pressure guidelines that have been issued over the past several years, the results of the current study might offer an evidence-based solution to realize the benefits of intensive treatment while minimizing harm. Furthermore, the ACC/AHA CVD risk estimate is a commonly used tool in current clinical practice, often integrated into electronic medical records, which would allow for clinicians to easily identify patients that are most likely to benefit from intensive blood pressure treatment. In those SPRINT-eligible patients with a 10-year CVD risk of ≥18.2%, treatment to an office SBP goal of <130 mm Hg would be recommended, consistent with the ACC/AHA 2017 blood pressure guidelines. In contrast, and consistent with the 2015 JNC8 and 2017 ACP/AAFP blood pressure guidelines, those with a 10-year CVD risk <18.2% would have a less aggressive SBP goal of <140 mm Hg.

STUDY LIMITATIONS. First, comparing the effectiveness of intensive versus standard treatment based on baseline CVD risk was not a pre-specified analysis of the SPRINT trial. Second, although lipid management has taken overall risk into account for the past decade, taking CVD risk into account when determining the appropriateness or intensity of blood pressure treatment is an emerging concept that has not been tested by randomized controlled trials (17). In support of this approach, several analyses have shown that although blood pressure lowering yields similar relative risk reduction irrespective of baseline CVD risk, those with the greatest baseline CVD risk have the greatest absolute risk reduction (19,20). In addition, if treatment of hypertension is based solely on blood pressure level, a large group of patients at risk for cardiovascular events would not receive antihypertensive therapy based on current guidelines (21). Citing this and other evidence, the 2017 ACC/AHA blood pressure guidelines support taking risk for cardiovascular events into account for the management of high blood pressure; however, further research is needed to determine appropriate risk-based guidance.

CONCLUSIONS

This study suggests that in adult patients with hypertension, those with a 10-year risk for CVD ≥18.2% would achieve more benefit than harm from intensive

treatment, whereas for those with a risk <18.2%, a standard blood pressure goal would be an appropriate management approach (**Central Illustration**). This analysis may help providers and patients make decisions regarding the intensity of blood pressure treatment to prevent cardiovascular events and death in adults with hypertension.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Based on data from the SPRINT trial, adults with hypertension whose 10-year risk of cardiovascular events is ≥18.2% gain more benefit than harm from targeting systolic BP <130 mm Hg; while for those whose risk is <18.2%, <140 mm Hg is an appropriate target.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to confirm whether these projections translate directly to clinical practice and how they may be modified by specific antihypertensive treatment regimens.

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