Clinical Research in Cardiology (2019) 108:273–281
https://doi.org/10.1007/s00392-018-1353-9

ORIGINAL PAPER

Influence of baseline systolic blood pressure on the relationship between intensive blood pressure control and cardiovascular outcomes in the Systolic Blood Pressure Intervention Trial (SPRINT)

Xiuting Sun[1,2] · Yue Guo[1,2] · Zhiqiang Nie[3,4] · Jing Cheng[5] · Huimin Zhou[1,2] · Xiangbin Zhong[1,2] · Shaozhan Zhang[1,2] · Zhimin Du[1,2] · Xiaodong Zhuang[1,2] · Xinxue Liao[1,2]

Received: 3 June 2018 / Accepted: 8 August 2018 / Published online: 24 August 2018

Abstract

Objective To determine whether the effects of intensive (< 120 mmHg) compared with standard (< 140 mmHg) systolic blood pressure (SBP) treatments are different among those with different baseline SBP.

Methods De-identified SPRINT database was used for this post hoc analysis. SPRINT participants were categorized by baseline SBP status, defined as high-SBP (≥ 140 mmHg) group versus the low-SBP (< 140 mmHg) group. The primary outcome was a composite of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes. Treatment-related adverse events including hypotension, syncope, and bradycardia were also evaluated. Cox regression was used to calculate hazard ratios for study outcomes with intensive compared with standard SBP treatment between these two groups.

Results Among 9361 participants randomized (age 67.9 ± 9.4 years; 35.5% female), 4964 and 4397 had baseline low SBP (< 140 mmHg) and high SBP (≥ 140 mmHg), respectively. After a median follow-up of 3.26 years, the hazard ratio for the primary outcome was 0.65 (95% CI 0.50, 0.83) and 0.84 (95% CI 0.66, 1.06) among those in the low-SBP group and high-SBP group, respectively (*P* value for interaction 0.15). For treatment-related adverse events, the hazard ratio with intensive SBP treatment was 2.03 (95% CI 1.44, 2.85) for the low-SBP group and 1.80 (95% CI 1.32, 2.47) for the high-SBP group (*P* value for interaction 0.28).

Conclusions Hypertensive patients with low baseline SBP may benefit from intensive SBP lowering, whereas benefits were inconclusive among those with high baseline SBP.

Keywords Systolic blood pressure · Intensive · Hypertension

Introduction

Hypertension (HT) is the leading cause of disability-adjusted life years and mortality worldwide, affecting nearly 30% of the adult population in Western countries [1]. Systolic blood

Xiuting Sun and Yue Guo contributed equally to the study.

✉ Xiaodong Zhuang
zhuangxd3@mail.sysu.edu.cn

✉ Xinxue Liao
liaoxinx@mail.sysu.edu.cn

1 Department of Cardiology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China

2 Key Laboratory of Assisted Circulation, Ministry of Health, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

3 Department of Epidemiology, Guangdong Cardiovascular Institute, Guangzhou, Guangdong, China

4 Key Laboratory of South China Structural Heart Disease, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

5 Laboratory Medicine Department, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

pressure (SBP) is a very important and independent risk predictor for coronary events, stroke and heart failure [2, 3]. Previous studies showed that for patients at all levels of baseline cardiovascular risk, treatment with any currently used drugs to lower SBP could reduce the risk of total major cardiovascular events (MACE) [4, 5]. The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated significant decreases in cardiovascular events and total mortality with intensive SBP lowering in adults with high cardiovascular risk in the absence of diabetes, but these benefits were accompanied by increased risk of adverse events. Later on, the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults has been providing recommendations for lower BP medication initiation thresholds (130/80 mmHg) and BP target goals.

However, controversy still exists as to the proper target BP for hypertensive individuals with different diseases and baseline characteristics [6]. Results from a recent study suggested that a target SBP of < 120 mmHg and diastolic blood pressure (DBP) < 70 mmHg were associated with more cardiovascular disease events in high-risk patients [7]. Moreover, among patients with heart failure, no significant differences were observed in the low BP target group [8, 9]. Wang et al. identified a small subgroup of SPRINT (baseline SBP > 160 mmHg, Framingham Risk Score (FRS) < 31%), who had a threefold increase in the risk of mortality with lower SBP target (< 120 mmHg) [9].

Thus, in patients with higher baseline SBP, the potential benefits or risks of intensive SBP lowering treatment are unclear. Therefore, we conducted a post hoc analysis of the SPRINT to examine whether the effects of intensive SBP control on cardiovascular events and adverse events are modified by baseline SBP categories.

Methods

SPRINT data and study population

This was a post hoc analysis of SPRINT. Limited SPRINT data were obtained from the National Heart, Lung, and Blood Institute (NHLBI) Data Repository for reproducing and replicating the results of this analysis. SPRINT was a randomized, controlled, open-label trial that compared the effects of intensive (SBP target < 120 mmHg) versus standard (SBP target < 140 mmHg) BP control in 9361 participants from the USA and Puerto Rico.

Participants in SPRINT were at least 50 years old, with an SBP 130–180 mmHg and an increased risk of CVD, which was defined by at least one of the following: clinical or subclinical CVD other than stroke; age ≥ 75 years; an FRS for 10-year cardiovascular disease risk ≥ 15%; chronic kidney disease (CKD), estimated glomerular filtration rate (eGFR) 20 to < 60 ml/min/1.73 m^2. Major exclusion criteria included diabetes mellitus, prior stroke, advanced CKD (eGFR < 20 ml/min/1.73 m^2), proteinuria > 1 g/day, polycystic kidney disease, and congestive heart failure (HF) [10]. The design, eligibility, and baseline characteristics of SPRINT have been described, and detailed inclusion and exclusion criteria listed in the SPRINT design paper [11].

Interventions and measurements

Participants were randomly assigned to intensive or standard group. Participants were seen monthly for the first 3 months and then every 3 months thereafter. All major classes of antihypertensive drugs were included in the formulary. Medications were adjusted to target an SBP < 120 mmHg in the intensive-treatment group and 135–139 mmHg in the standard treatment group.

Data were collected at baseline for every participant. Clinical and laboratory data were obtained at baseline and every 3 months thereafter and quarterly thereafter for measurement of serum creatinine. An automated measurement system (Model 907, Omron Healthcare) was used to record BP at the clinic visit after the participant had been seated for 5 min of quiet rest. The mean of three office BP measurements was used to estimate BP. A structured interview was used every 3 months in both groups to get self-reported cardiovascular disease outcomes [11].

Clinical outcomes

The primary cardiovascular disease outcome was a composite of nonfatal myocardial infarction (MI), acute coronary syndrome (ACS) not resulting in a MI, nonfatal stroke, nonfatal acute decompensated HF, and death from cardiovascular causes. The secondary outcomes included the individual components of the primary outcome and death from any cause [10, 11].

Serious adverse events

Serious adverse events (SAEs) were defined as events that were fatal or life threatening, resulted in significant or persistent disability, required hospitalization, or resulted in prolonged hospitalization or medical events that the investigator judged to be a significant hazard or harm to the participant and required medical or surgical intervention to prevent any of these. The following conditions were reported as adverse events if they were evaluated in an emergency department: hypotension, syncope, bradycardia, and acute renal failure [10, 11].

Statistical analysis

Baseline characteristics were compared across treatment arms stratified by those with baseline high SBP, defined as baseline SBP ≥ 140 mmHg, versus those with low SBP, defined as baseline SBP < 140 mmHg using ANOVA for continuous variables and Chi square tests for categorical variables. Baseline characteristics were also compared between those with low SBP and high SBP at baseline regardless of randomized treatment assignment.

Using the intention-to-treat approach for all randomly assigned participants with two-sided tests at the 5% level of significance, we used Cox proportional hazards regression with stratification according to baseline low-SBP versus high-SBP status at baseline, to calculate hazard ratios (HR) for the primary outcome associated with intensive SBP treatment versus standard SBP treatment (reference) among those with low SBP or high SBP at baseline. We tested the proportional hazards assumption by modeling the product of SBP treatment arm and the log of follow-up time as an interaction term; no violations were observed. To assess for effect modification of treatment arm among SPRINT participants with baseline SBP, we included the product term (SBP treatment arm × high SBP or low SBP) in the Cox proportional hazards regression in the full sample using a likelihood ratio test. We adjusted age, sex, FRS, smoking status, body mass index (BMI), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), albumin-to-creatinine ratio (ALCR), history of CKD and CVD, and use of statin or anti-HT medication. Measures of interaction for the primary outcome are presented on both the additive and multiplicative scales. Additionally, we modeled SBP as restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of its distribution to provide a smooth, yet flexible description of the dose–response relationship between SBP and primary outcome. Moreover, we did landmark analyses to assess outcomes and estimated differences between groups. Furthermore, we divided participants into six groups (< 120, 120–130, 130–140, 150–160, and > 160 mmHg) to calculate HR for the primary outcome. All tests were two-sided, and the significance level chosen was $P < 0.05$. All analysis was done using R 3.3.0 (http://www.R-project.org).

Results

Among 9361 participants, 4964 and 4397 had baseline low SBP (< 140 mmHg) and high SBP (≥ 140 mmHg), respectively. The median follow-up was 3.26 years (interquartile range 2.79–3.79 years). The distribution of baseline SBP (140.0 ± 15.5 mmHg) is shown in Fig. 1. The baseline characteristics of the SPRINT study population by treatment arm within the low-SBP (< 140 mmHg) and high-SBP (≥ 140 mmHg) groups are shown in Table 1. Compared with the low-SBP group, participants in the high-SBP group were older and complicated with higher DBP, FRS, total cholesterol (TC), FPG, and BMI. However, there were no obvious differences among TG, smoking status, and history of CVD or CKD.

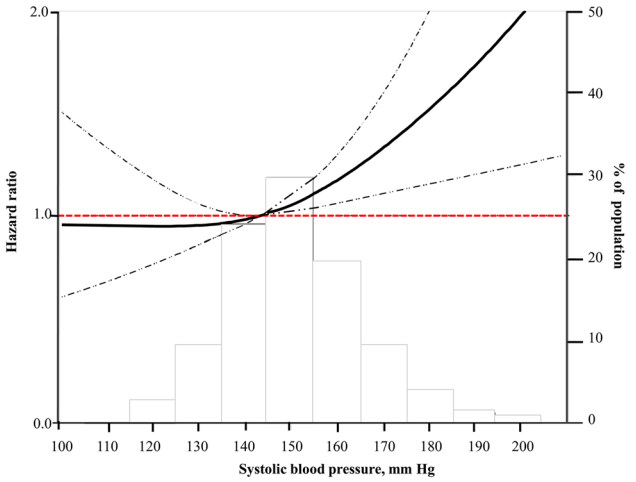

Fig. 1 Hazard ratios for sudden cardiac death by levels of baseline SBP

Spline regression analysis also confirmed that baseline SBP was associated with the risk of primary outcome, with an approximately linear dose–response relationship (*P* value for non-linear spline terms > 0.85; Fig. 1). As shown in Table 2, after a median follow-up of 3.26 years, the HR for the primary outcome was 0.65 (95% CI 0.50–0.83) and 0.84 (95% CI 0.66–1.06) among those in the low-SBP group and high-SBP group, respectively (*P* value for interaction 0.19) (Fig. 2). The landmark analysis in the high-SBP group showed that the HR for the primary outcome was 1.02 (95% CI 0.76–1.36) and 0.61 (95% CI 0.41–0.90) within and after first 2 years, respectively. For CV death, the HR was 0.68 (95% CI 0.50–0.92) if baseline SBP < 140 mmHg, whereas the HR was 0.80 (95% CI 0.60–1.08) when baseline SBP was 140 mmHg or above. Similarly, the landmark analysis showed that the HR for the CV cause death in the high-SBP group was 0.87 (95% CI 0.74–1.83) and 0.39 (95% CI 0.19–0.87) within and after first 2 years, respectively (Fig. 2). The beneficial effects of intensive treatment were obvious only in the low-SBP group in most of the clinical outcomes.

Among participants with CKD, there were no significant differences of intensive blood pressure treatment in long-term dialysis and albuminuria between the low-SBP and high-SBP groups. However, among participants without CKD, the HR for albuminuria was 0.70 (95% CI 0.50, 0.98) and 0.83 (95% CI 0.64, 1.07) among those in the

Table 1 Baseline characteristics of participants overall and those with SBP < 140 and ≥ 140 mmHg

Characteristics	Baseline SBP, mmHg				Baseline SBP, mmHg		*P* value
	Low SBP < 140		High SBP ≥ 140		Low SBP < 140	High SBP ≥ 140	
	Intensive	Standard	Intensive	Standard			
N	2482	2482	2196	2201	4964	4397	
Age, years	67.3 ± 8.9	67.2 ± 9.2	68.6 ± 9.7	68.6 ± 9.7	67.2 ± 9.1	68.6 ± 9.7	< 0.001
Female	815 (32.8%)	789 (31.8%)	869 (39.6%)	859 (39.0%)	1604 (32.3%)	1728 (39.3%)	< 0.001
FRS, %	16.7 ± 8.9	16.7 ± 8.8	23.8 ± 11.6	23.9 ± 11.5	16.7 ± 8.8	23.8 ± 11.5	< 0.001
Smoking status							0.272
Never	1075 (43.3%)	1087 (43.8%)	975 (44.4%)	985 (44.8%)	2162 (43.6%)	1960 (44.6%)	
Former	1067 (43.0%)	1084 (43.7%)	910 (41.4%)	912 (41.4%)	2151 (43.3%)	1822 (41.4%)	
Current	333 (13.4%)	304 (12.3%)	306 (13.9%)	297 (13.5%)	637 (12.8%)	603 (13.7%)	
SBP, mmHg	128.1 ± 8.5	128.3 ± 8.2	152.7 ± 11.2	152.4 ± 10.9	128.2 ± 8.4	152.5 ± 11.1	< 0.001
DBP, mmHg	73.9 ± 9.9	73.9 ± 10.0	83.0 ± 12.0	82.7 ± 12.3	73.9 ± 10.0	82.8 ± 12.1	< 0.001
BMI, kg/m^2	30.1 ± 5.7	30.1 ± 5.8	29.6 ± 5.8	29.3 ± 5.6	30.1 ± 5.7	29.4 ± 5.7	< 0.001
LDL-C, mg/dl	187.5 ± 41.1	186.6 ± 41.0	193.2 ± 41.4	193.9 ± 40.5	187.0 ± 41.0	193.5 ± 40.9	< 0.001
HDL-C, mg/dl	51.8 ± 13.7	51.7 ± 13.8	54.2 ± 14.9	54.0 ± 15.4	51.8 ± 13.7	54.1 ± 15.2	< 0.001
TG, mg/dl	125.2 ± 94.2	127.1 ± 100.1	124.5 ± 75.2	127.1 ± 88.9	126.0 ± 97.2	125.8 ± 82.3	0.910
glucose, mg/dl	99.0 ± 13.3	99.3 ± 14.2	98.5 ± 14.1	98.1 ± 12.2	99.2 ± 13.8	98.3 ± 13.2	0.002
ALCR, mg/g	36.4 ± 174.6	31.2 ± 132.5	52.8 ± 182.8	52.1 ± 172.4	33.8 ± 155.0	52.5 ± 177.7	< 0.001
CKD history	716 (28.9%)	716 (28.9%)	614 (28.0%)	600 (27.3%)	1432 (28.9%)	1214 (27.6%)	0.184
CVD history	500 (20.2%)	537 (21.6%)	440 (20.0%)	400 (18.2%)	1037 (20.9%)	840 (19.1%)	0.031
N_AGENTS							< 0.001
0	167 (6.7%)	179 (7.2%)	265 (12.1%)	271 (12.3%)	346 (7.0%)	536 (12.2%)	
1	693 (27.9%)	741 (29.9%)	672 (30.6%)	647 (29.4%)	1434 (28.9%)	1319 (30.0%)	
2	931 (37.5%)	914 (36.8%)	734 (33.4%)	713 (32.4%)	1845 (37.2%)	1447 (32.9%)	
3	542 (21.8%)	508 (20.5%)	414 (18.9%)	456 (20.7%)	1050 (21.2%)	870 (19.8%)	
4	144 (5.8%)	133 (5.4%)	109 (5.0%)	111 (5.0%)	277 (5.6%)	220 (5.0%)	
5	4 (0.2%)	7 (0.3%)	2 (0.1%)	3 (0.1%)	11 (0.2%)	5 (0.1%)	
Statin	1126 (45.7%)	1206 (49.0%)	852 (39.1%)	870 (39.9%)	2332 (47.3%)	1722 (39.5%)	< 0.001

Values are mean ± SD or number (%)

FRS Framingham Risk Score, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *LDL-C* low density lipoprotein cholesterol, *HDL-C* high density lipoprotein cholesterol, *TG* triglycerides, *ALCR* albumin-to-creatinine ratio, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *N_AGENTS* number of antihypertensive agents

low-SBP group and high-SBP group, whereas the HR for eGFR ≥ 30% reduction was significantly increased in both the groups: 5.95 (95% CI 2.81, 12.60) and 2.91 (95% CI 1.89, 4.48), respectively.

Information regarding SAEs is summarized in Table 2. The incidence of treatment-related SAEs was lower (3.16%, 157/4964) in the low-SBP group compared with the high-SBP group (4.12%, 181/4397). For treatment-related SAEs, the HR with intensive SBP treatment was 2.03 (95% CI 1.44–2.85) for the low-SBP group and 1.80 (95% CI 1.32–2.47) for the high-SBP group. Intensive treatment was associated with a higher incidence of adverse events, including acute kidney injury, hypotension, syncope, and bradycardia (Table 2).

Discussion

Our study indicated that the benefits of intensive SBP lowering may only be evident among those with low SBP (< 140 mmHg) at baseline. For participants with high baseline SBP, intensive treatment showed no improvement in clinical outcomes, but generated more adverse events versus standard treatment. Since most participants in SPRINT already took antihypertensive medication at baseline, our finding implied that a lower targeted SBP may not be applicable to patients with considerably higher baseline SBP in SPRINT.

Table 2 Incidence rates and hazard ratios for the primary and secondary outcomes by treatment arm

	Low SBP < 140, mmHg			High SBP ≥ 140, mmHg		
	Intensive	Standard	HR and 95% CI	Intensive	Standard	HR and 95% CI
N	2482	2482		2196	2201	
Primary outcome	110 (4.43%)	160 (6.45%)	0.65 (0.50, 0.83)	133 (6.06%)	159 (7.22%)	0.84 (0.66, 1.06)
Secondary outcomes						
Myocardial infarction	50 (2.01%)	53 (2.14%)	0.92 (0.62, 1.36)	47 (2.14%)	63 (2.86%)	0.74 (0.50, 1.09)
ACS	14 (0.56%)	29 (1.17%)	0.47 (0.25, 0.89)	26 (1.18%)	11 (0.50%)	2.69 (1.26, 5.76)
Stroke	22 (0.89%)	28 (1.13%)	0.77 (0.44, 1.35)	40 (1.82%)	42 (1.91%)	0.88 (0.56, 1.37)
Heart failure	23 (0.93%)	48 (1.93%)	0.39 (0.23, 0.66)	39 (1.78%)	52 (2.36%)	0.77 (0.50, 1.18)
CVD death	16 (0.64%)	29 (1.17%)	0.58 (0.31, 1.10)	21 (0.96%)	36 (1.64%)	0.56 (0.32, 0.98)
All-cause death	71 (2.86%)	103 (4.15%)	0.68 (0.50, 0.92)	84 (3.83%)	107 (4.86%)	0.80 (0.60, 1.08)
Participants with CKD						
Long-term dialysis	4 (0.56%)	5 (0.70%)	0.78 (0.21, 2.93)	2 (0.33%)	5 (0.83%)	0.61 (0.22, 1.67)
Albuminuria	33 (10.09%)	46 (14.79%)	0.66 (0.42, 1.03)	16 (8.04%)	13 (6.88%)	0.77 (0.53, 1.13)
Participants without CKD						
eGFR ≥ 30% reduction	47 (2.68%)	9 (0.51%)	5.95 (2.81, 12.60)	80 (5.07%)	28 (1.76%)	2.91 (1.89, 4.48)
Albuminuria	62 (5.84%)	85 (7.97%)	0.70 (0.50, 0.98)	48 (6.79%)	50 (6.54%)	0.83 (0.64, 1.07)
Safety outcomes						
Related SAE event	108 (4.35%)	49 (1.97%)	2.03 (1.44, 2.85)	112 (5.10%)	69 (3.13%)	1.80 (1.32, 2.47)
AKI	90 (3.63%)	51 (2.05%)	1.62 (1.15, 2.27)	103 (4.69%)	66 (3.00%)	1.75 (1.28, 2.39)
Hypotension	59 (2.38%)	32 (1.29%)	1.77 (1.15, 2.73)	51 (2.32%)	34 (1.54%)	1.74 (1.11, 2.74)
Syncope	52 (2.10%)	39 (1.57%)	1.27 (0.83, 1.96)	55 (2.50%)	41 (1.86%)	1.49 (0.98, 2.26)
Bradycardia	45 (1.81%)	35 (1.41%)	1.25 (0.81, 1.91)	42 (1.91%)	38 (1.73%)	1.37 (0.90, 2.09)

Values are mean ± SD or number (%)

SBP systolic blood pressure, *HR* hazard ratio, *CI* confidence interval, *ACS* acute coronary syndrome, *CVD* cardiovascular disease, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *SAE* severe adverse events, *AKI* acute kidney injury

Moreover, in our study, we found obvious differences in baseline characteristics between the two groups. Participants in the standard group were more complicated at baseline, including older age, higher SBP, DBP, TC, FPG, and greater overall CV risk. Thus, for those patients, more individualized and systematic treatment was required. The findings of baseline SBP disparities were important in the study to understand intensive treatment was no better than standard in the participants with high baseline SBP. Baseline SBP is one of the most important prognostic indicators for patients with high cardiovascular risk [12]. Our data indicated that baseline SBP should be paid more attention to in future research, for a proper SBP target to be determined for hypertensives.

SPRINT demonstrated targeting an SBP of < 120 mmHg compared with < 140 mmHg in patients with hypertension, but without diabetes, reduced major cardiovascular events by 25% and death from any cause by 27% [10]. During the past 2 years, several subgroup (including age, race, and baseline fasting serum glucose, etc.) analyses of SPRINT have been published, among which most researchers found that intensive target was better than standard target for those patients in different subgroups [13–15]. Of note, a previous analysis showed that the cardiovascular benefit from intensive treatment was attenuated in patients with lower eGFR, indicating Intensive BP control may provide little or no benefit and even be harmful for patients with moderate-to-advanced chronic kidney disease [16]. However, based on previous studies, there were different goals for different hypertensive patients, like elderly, previous stroke, high cardiovascular risk, and diabetes [17]. Recently, a post hoc study of SPRINT showed low baseline DBP was associated with increased risk of CVD events [18]. There is still uncertainty as to whether the benefits of intensive SBP lowering extend to hypertensives with high baseline SBP. Our data provided new evidence on a less aggressive target (< 140 mmHg) for patients with high SBP at baseline.

Our results were consistent with a recently published systematic review which showed that only in patients with baseline SBP ≥ 140 mmHg, treatment was associated with reduced a risk for death and MACE. Brunström et al. investigated 74 trials and found that the effect of BP lowering significantly interacted with baseline SBP [19]. The ACCORD trial showed that in patients with type 2 diabetes at high risk for cardiovascular events, targeting an SBP of < 120 mmHg compared with < 140 mmHg did not

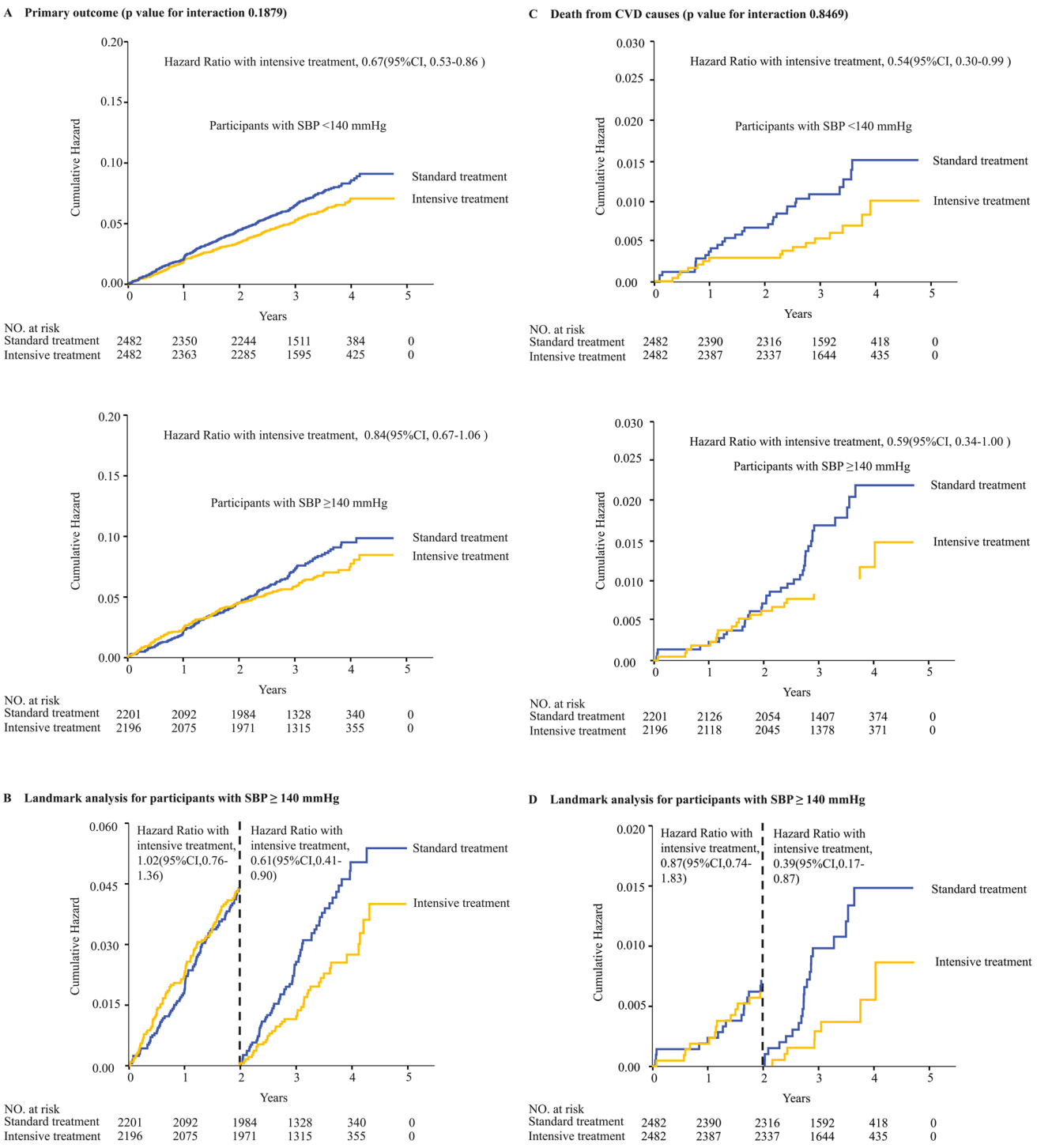

Fig. 2 Cumulative incidence of the primary outcome (**A**), CVD mortality (**C**) by treatment arm stratified by baseline SBP; and landmark analysis of intensive treatment for high-SBP group (**B**, **D**)

reduce the rate of MACE [20]. Waits et al. studied 6107 participants without prior cardiovascular disease (CVD) and found that DBP < 70 mmHg carried higher risk of subclinical myocardial injury [21]. Also, results from ONTARGET, TRANSCEND, and VALUE trials showed patients with a target SBP between 120 and 140 mmHg have the lowest risk for primary cardiovascular outcome [7, 22]. Moreover, a meta-analysis of BP-lowering trials suggested that lowering SBP/DBP to < 130/80 versus < 140/90 mmHg did not reduce MACE [23]. Earlier

studies in patients with acute intracerebral hemorrhage noted that a standard target was better than intensive treatment [24–26]. Combined with the previous studies, we determined intensive treatment in the high-SBP group reduced the risk for the cardiovascular outcomes, and a target of < 140 mmHg may be enough for patients with high baseline SBP.

The reasons for our unexpected results are unclear. Several factors may possibly contribute to our findings: First, the trial did not enroll persons with type 2 diabetes or prevalent stroke. Younger individuals with HT at high risk for CVD and those with an average SBP of 130–139 mmHg who have a Framingham 10-year CVD risk score < 15% were also excluded [27]. Secondly, most participants were already taking antihypertensive medicine; the "blood pressure memory" may play an important role in the process of reaching the target SBP among patients with high baseline SBP. Although SPRINT showed significant benefit of intensive BP reduction on cardiovascular events, the generalizability of SPRINT findings to population should be considered carefully [28–30]. Finally, aggressive SBP lowering may be harmful for those people with high baseline SBP [31, 32].

So far, controversy still exits regarding a proper BP target for hypertensives. More and more doctors tend to take individual treatment. 2017 ACC guideline of HT recommended a BP target of less than 130/80 mmHg, for both hypertensives with known CVD or 10-year ASCVD event risk ≥ 10% or without additional markers of increased CVD risk [33]. Some previous studies showed that intensive treatment resulted in more cardiovascular benefits [34–36]. Ettehad et al. identified 123 studies with 613,815 participants and found that a 10 mmHg reduction in SBP reduced the risk of MACE by 20%, CAD by 17%, stroke by 27%, heart failure by 28%, and all-cause mortality by 13% [36]. As aggressive BP lowering required more drugs and could result in more SAEs, renal denervation may serve as a new and promising method in addition to traditional anti-HT drugs for clinicians to treat HT [37, 38]. Based on all studies mentioned in this article, individualized SBP target together may be better than the universal one for patients.

The strength of the current analysis was our ability to examine the association of baseline SBP and treatment target of SBP, contributing additional information on SBP management strategies beyond SPRINT. Our results provided new evidence regarding the efficacy of standard blood pressure lowering efforts on patients with high baseline SBP. In addition, the results of our study were from well-designed SPRINT, in which rigorous study methods were used to collect the data. So, these results are representative of the US noninstitutionalized civilian population.

Limitations

Several limitations of our study should be considered. First, this was a post hoc analysis of SPRINT. As with even the largest clinical trials, the power for interaction and subgroup analyses is small. Secondly, the SPRINT trial did not enroll persons with type 2 diabetes, prevalent stroke, or younger individuals with HT at high risk for CVD. In addition, therefore, confirmation in prospectively planned trials is required in the future.

Conclusions

In conclusion, patients with low baseline SBP may benefit from intensive SBP lowering, whereas benefits were inconclusive among those with high baseline SBP. This finding should be prospectively tested to better engage intensive SBP treatment patients in decision making and to improve outcomes.

Author contributions LXX and ZXX had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: LXX, ZXD, SXT, GY, DZM. Acquisition, analysis, or interpretation of data: NZQ, SXT, ZSZ, ZHM, DZM. Drafting of the manuscript: ZXD, LXX, SXT. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: NZQ, SXT, ZXB. Obtained funding: LXX, ZXD. Administrative, technical, or material support: ZXD.

Funding This study was supported by the Natural Science Foundation of Guangdong Province (2016A030310140/20160903) to LXX, and the Natural Science Foundations of China (Grant no. 81600206) to ZXD.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

References

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J (2005) Global burden of hypertension: analysis of worldwide data. Lancet 365(9455):217–223. https://doi.org/10.1016/S0140-6736(05)17741-1
2. Liu FD, Shen XL, Zhao R et al. Pulse pressure as an independent predictor of stroke: a systematic review and a meta-analysis. Clin Res Cardiol 2016;105(8): 677–686. https://doi.org/10.1007/s00392-016-0972-2
3. Collins R, Peto R, Macmahon S, Hebert P (1990) et al. Blood pressure, stroke, and coronary heart disease. Part 2, short-term reduction in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 335:827–838
4. Sundstr MJ, Arima H, Woodward M et al (2014) Blood pressure-lowering treatment based on cardiovascular risk: a

meta-analysis of individual patient data. Lancet 384(9943):591–598. https://doi.org/10.1016/S0140-6736(14)61212-5
5. Turnbull F (2003) Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 362(9395):1527–1535. https://doi.org/10.1016/S0140-6736(03)14739-3
6. Kulenthiran S, Ewen S, Böhm M et al (2017) Hypertension up to date: SPRINT to SPYRAL. Clin Res Cardiol 106(7):475–484. https://doi.org/10.1007/s00392-017-1095-0
7. Bohm M, Schumacher H, Teo KK et al (2017) Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. Lancet 389(10085):2226–2237. https://doi.org/10.1016/S0140-6736(17)30754-7
8. Cotter G, Davison BA, Butler J et al (2018) Relationship between baseline systolic blood pressure and long-term outcomes in acute heart failure patients treated with TRV027: an exploratory subgroup analysis of BLAST-AHF. Clin Res Cardiol 107(2):170–181. https://doi.org/10.1007/s00392-017-1168-0
9. Wang TD, Lin HJ, Chen WJ, Weng TC, Shau WY (2017) Increased all-cause mortality with intensive blood-pressure control in patients with a baseline systolic blood pressure of ≥ 160 mmHg and a Lower Framingham risk score: a cautionary note from SPRINT. In: Presentation at: annual meeting of the European Society of Cardiology, August 28, 2017, Barcelona
10. Group TSR (2015) A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373(22):2103–2116. https://doi.org/10.1056/NEJMoa1511939
11. Ambrosius WT, Sink KM, Foy CG et al (2014) The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the systolic blood pressure intervention trial (SPRINT). Clin Trials 11(5):532–546. https://doi.org/10.1177/1740774514537404
12. Kajimoto K, Sato N, Takano T (2015) Association of age and baseline systolic blood pressure with outcomes in patients hospitalized for acute heart failure syndromes. Int J Cardiol 191:100–106. https://doi.org/10.1016/j.ijcard.2015.04.258
13. Weiner DE, Gaussoin SA, Nord J et al (2017) Cognitive function and kidney disease: baseline data from the systolic blood pressure intervention trial (SPRINT). Am J Kidney Dis 70(3):357–367. https://doi.org/10.1053/j.ajkd.2017.04.021
14. Williamson JD, Supiano MA, Applegate WB et al (2016) Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥ 75 years. JAMA 315(24):2673–2682. https://doi.org/10.1001/jama.2016.7050
15. Bress AP, King JB, Kreider KE et al (2017) Effect of intensive versus standard blood pressure treatment according to baseline prediabetes status: a post hoc analysis of a randomized trial. Diabetes Care. https://doi.org/10.2337/dc17-0885
16. Obi Y, Kalantar-Zadeh K, Shintani A, Kovesdy CP, Hamano T (2018) Estimated glomerular filtration rate and the risk-benefit profile of intensive blood pressure control amongst nondiabetic patients: a post hoc analysis of a randomized clinical trial. J Intern Med 283(3):314–327. https://doi.org/10.1111/joim.12701
17. Zanchetti A, Grassi G, Mancia G (2009) When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. J Hypertens 27:923–934. https://doi.org/10.1097/HJH.0b013e32832aa6b5
18. Srinivasan B, Glenn MC, Alfred K, Cheung et al (2017) Influence of baseline diastolic blood pressure on effects of intensive compared to standard blood pressure control. Circulation 137(2):134–143. https://doi.org/10.1161/CIRCULATIONAHA.117.030848
19. Brunström M, Carlberg B (2017) Association of blood pressure lowering with mortality and cardiovascular disease across blood pressure levels. JAMA Intern Med 177(10):1498–1505. https://doi.org/10.1001/jamainternmed.2017.4377
20. Group AS, Cushman WC, Evans GW, Byington RP, Goff D Jr (2010) Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 362(17):1575–1585. https://doi.org/10.1056/NEJMoa1001286
21. Waits GS, O'Neal WT, Sandesara PB, Li Y, Shah AJ, Soliman EZ (2018) Association between low diastolic blood pressure and subclinical myocardial injury. Clin Res Cardiol 107(4):312–318. https://doi.org/10.1007/s00392-017-1184-0
22. Mancia G, Kjeldsen SE, Zappe DH, Holzhauer B, Hua TA (2016) Cardiovascular outcomes at different on-treatment blood pressures in the hypertensive patients of the VALUE trial. Eur Heart J. 37:955–964. https://doi.org/10.1093/eurheartj/ehv633
23. Thomopoulos C, Parati G, Zanchetti A (2014) Effects of blood pressure lowering on outcome incidence in hypertension. J Hypertens 32(12):2296–2304. https://doi.org/10.1097/HJH.0000000000000379
24. Nishikawa T, Ueba T, Kajiwara M, Iwata R, Miyamatsu N, Yamashita K (2010) Preventive effect of aggressive blood pressure lowering on hematoma enlargement in patients with ultra-acute intracerebral hemorrhage. Neurol Med Chir (Tokyo) 50(11):966–971. https://doi.org/10.2176/nmc.50.966
25. Sakamoto Y, Koga M, Todo K et al (2015) Relative systolic blood pressure reduction and clinical outcomes in hyperacute intracerebral hemorrhage. J Hypertens 33(5):1069–1073. https://doi.org/10.1097/HJH.0000000000000512
26. Anderson CS, Selim MH, Molina CA, Qureshi AI (2017) Intensive blood pressure lowering in intracerebral hemorrhage. Stroke 48:2034–2037. https://doi.org/10.1161/STROKEAHA.117.016185
27. Cushman WC, Whelton PK, Fine LJ et al (2015) SPRINT trial results latest news in hypertension management. Hypertension 2(67):263–265. https://doi.org/10.1161/HYPERTENSIONAHA.115.06722
28. Bress AP, Tanner RM, Hess R, Colantonio LD, Shimbo D, Muntner P (2016) Generalizability of SPRINT results to the U.S. adult population. J Am Coll Cardiol 67(5):463–472. https://doi.org/10.1016/j.jacc.2015.10.037
29. Bhatt H, Ghazi L, Calhoun D, Oparil S (2016) BP targets in hypertension: what should we do now that SPRINT is out? Curr Cardiol Rep 18(10):98. https://doi.org/10.1007/s11886-016-0775-0
30. Jones DW, Weatherly L, Hall JE (2016) SPRINT what remains unanswered and where do we go from here? Hypertension 67:261–262. https://doi.org/10.1161/HYPERTENSIONAHA.115.06723
31. Sakamoto Y, Koga M, Yamagami H et al (2013) Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: the stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. Stroke 44(7):1846–1851. https://doi.org/10.1161/STROKEAHA.113.001212
32. Verdecchia P, Angeli F, Mazzotta G, Garofoli M, Reboldi G (2013) aggressive blood pressure lowering is dangerous: the J-curve: con side of the argument. Hypertension 63(1):37–40. https://doi.org/10.1161/HYPERTENSIONAHA.113.01018
33. Whelton PK, Carey RM, Aronow WS et al (2017) 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. J Am Coll Cardiol 71(19):e127–e248. https://doi.org/10.1016/j.jacc.2017.11.006
34. Reboldi G, Angeli F, de Simone G, Staessen JA, Verdecchia P (2014) Tight versus standard blood pressure control in patients with hypertension with and without cardiovascular disease. Hypertension 63(3):475–482. https://doi.org/10.1161/HYPERTENSIONAHA.113.02089

35. Bundy JD, Li C, Stuchlik P et al (2017) Systolic blood pressure reduction and risk of cardiovascular disease and mortality. JAMA Cardiol 2(7):775–781. https://doi.org/10.1001/jamacardio.2017.1421
36. Ettehad D, Emdin CA, Kiran A et al (2016) Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 387(10022):957–967. https://doi.org/10.1016/S0140-6736(15)01225-8
37. De Jager RL, Sanders MF, Bots ML et al. Renal denervation in hypertensive patients not on blood pressure lowering drugs. Clin Res Cardiol 2016;105(9): 755–762. https://doi.org/10.1007/s00392-016-0984-y
38. Stoiber L, Mahfoud F, Zamani SM et al (2018) Renal sympathetic denervation restores aortic distensibility in patients with resistant hypertension: data from a multi-center trial. Clin Res Cardiol. https://doi.org/10.1007/s00392-018-1229-z **(Epub ahead of print)**