ORIGINAL RESEARCH

Low Diastolic Blood Pressure is Not Related to Risk of First Episode of Stroke in a High-Risk Population: A Secondary Analysis of SPRINT

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***Background*—**Hypertension is the most prevalent and leading risk factor for stroke. SPRINT (The Systolic Blood Pressure Intervention Trial) assessed the effects on cardiovascular event risk of intensive compared with standard systolic blood pressure reduction. In this secondary analysis of SPRINT data, we investigated how low on-treatment diastolic blood pressure (DBP) influenced risk for stroke events.

***Methods and Results*—**For this analysis, we used SPRINT_POP (Primary Outcome Paper) Research Materials from the National Heart, Lung and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center. Data for 8944 SPRINT participants were analyzed from the period after target blood pressure was achieved until the end of the trial. Overall, there were 110 stroke events, including 49 from the intensive-treatment arm and 61 in the standard-treatment group. In participants with DBP <70 mm Hg, stroke risk was higher than with DBP ≥70 mm Hg (hazard ratio, 1.467; 95% CI 1.009–2.133; *P*=0.0445). Univariable Cox proportional hazard risk analysis showed that in the whole group, age and cardiovascular and chronic renal diseases were stroke risk factors. These risk factors were related to lower DBP and higher pulse pressure, however, not to study arm. Multivariable Cox proportional hazard analysis revealed that only age, history of cardiovascular disease, current smoking status and on-treatment systolic blood pressure were significantly related to stroke risk.

***Conclusions*—**Low on-treatment DBP is not related to the risk for the first stroke, in contrast to older age, the history of cardiovascular disease, current smoking status, and on-treatment systolic blood pressure.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT01206062. **(*J Am Heart Assoc*. 2019;8: e010811. DOI: 10.1161/JAHA.118.010811.)**

Key Words: blood pressure • diastolic blood pressure • hypertension • J-shaped curve • SPRINT (Systolic Blood Pressure Intervention Trial) • stroke

Hypertension is the most prevalent treatable risk factor for stroke and other vascular events.[1,2] Observational studies have demonstrated that stroke risk decreases continuously as systolic blood pressure (SBP) decreases down to ≈115 mm Hg.[3] The magnitude of safe blood pressure (BP) reduction in stroke prevention has yet to be established in randomized trials. Benefits from tight BP control in the HOT (Hypertension Optimal Treatment) trial (<120/70 mm Hg) were not obvious.[4] In the population with diabetes mellitus in the ACCORD (Action to Control Cardiovascular Risk in Type 2 Diabetes) trial,[5] the group with tight BP control had fewer stroke events, but no benefit was seen for other end points. In a meta-analysis of tight versus normal BP control, Lee et al concluded that achieving an SBP <130 mm Hg compared with 130 to 139 mm Hg provided additional stroke protection only among people with risk factors.[6] The SPRINT (Systolic Blood Pressure Intervention Trial) results showed that achieving SBP <120 mm Hg, compared with <140 mm Hg, resulted in lower rates of fatal and non-fatal major cardiovascular events and death from any cause; however, stroke events were not decreased.[7]

In 1979, Stewart reported an association of lower diastolic BP (DBP) with increased myocardial infarction rates in patients with hypertension.[8–10] An increase in stroke risk in

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Clinical Perspective

What Is New?

- Low diastolic blood pressure (<70 mm Hg) is related to the first stroke incidence in hypertensive high cardiovascular risk subjects.
- The impact of low diastolic blood pressure on stroke risk is diminished by patient's characteristic, especially age, prior medical history, and smoking habits.

What Are the Clinical Implications?

- Among hypertensives at high cardiovascular risk, low diastolic blood pressure should not be an obstacle in achieving target systolic blood pressure when stroke risk reduction is considered.

the Rotterdam observational study began at DBP <65 mm Hg.[11] Other authors have proposed that the relationship between cardiovascular risk and BP reduction may follow a J-shaped curve.[12,13] However, the SHEP (Systolic Hypertension in the Elderly Program) trial found fewer stroke events with DBP <70 mm Hg achieved in the active treatment group.[14] Similarly, in the Hypertension in the Very Elderly Trial, which suggested a cause-and-effect relationship between lower DBP and adverse cerebrovascular outcomes, DBP <80 mm Hg was associated with a significant reduction in fatal stroke.[15] A linear rather than a J-shaped relationship between stroke events and BP has thus been postulated, but data from large, randomized controlled trials are needed to provide definitive answers.[16,17]

The SPRINT trial primary analyses did not present data on DBP, although the reduction in SBP also influences DBP. For this reason, in this secondary analysis of SPRINT data, we investigated how a low DBP influenced the first stroke occurrence in the SPRINT population.

Methods

SPRINT was a randomized, multicenter open-label trial evaluating how SBP reductions to <120 versus <140 mm Hg affected cardiovascular risk. In total, SPRINT enrolled 9361 participants. Through 3.26 years of follow-up, mean SBP values in the intensive and standard treatment arms were 121.5 mm Hg and 134.6 mm Hg, respectively in the intensive and standard treatment arm. A significant reduction in the primary outcome (a composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes) was found with intensive compared with standard treatment. The rationale, protocol, and results of SPRINT have been published and widely discussed elsewhere.[7,18]

Study Population

According to the SPRINT protocol we decided to analyze the interval from the 6-month visit until the end of the study because during this period, BP was relatively stable.[7,19] Figure 1 presents SBP and DBP over the duration of the trial with the analyzed study period highlighted. Our study included 8944 participants who were recognized as having high risk for cardiovascular diseases and events, with the following risk factors: older age, SBP 130 to 180 mm Hg, and a history of cardiovascular or chronic kidney disease or Framingham Risk Score for 10-year cardiovascular disease risk >15%. Inclusion and exclusion criteria are described elsewhere.[7] Participants were randomized to intensive (target SBP <120 mm Hg) or standard treatment (target SBP <140 mm Hg). A target DBP was not selected, although after meeting the goal for SBP, participants were treated to achieve DBP <90 mm Hg. The SPRINT study protocol assumed down-titration of antihypertensive agents if the SBP reached <130 mm Hg at a single visit or <135 mm Hg at 2 consecutive visits in the standard treatment arm regardless of DBP.[19]

BP and Clinical and Laboratory Measurements

SBP and DBP were measured 3 times during each visit using an automated office system (Model 907, Omron Healthcare), and the mean of those measurements was calculated. For

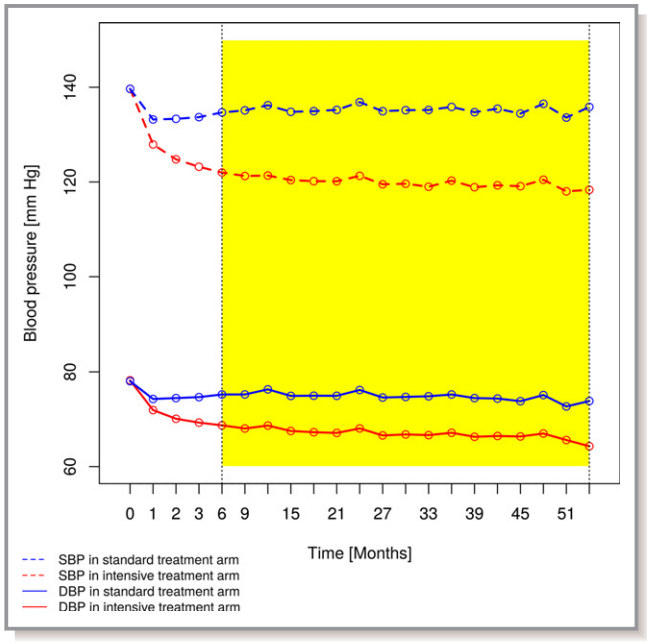

Figure 1. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) in standard and intensive treatment arms throughout the trial, with the current analysis period highlighted in yellow.

each individual, we calculated the median SBP and DBP measured at visits from the sixth month until the end of the study. For each study group, we calculated the mean of these medians. Anthropometric, laboratory, and other data collected during the original study were used, and pulse pressure was computed.[7]

The following events were defined as indicating clinical cardiovascular disease: previous myocardial infarction or acute coronary syndrome; percutaneous coronary intervention; coronary artery bypass grafting; carotid endarterectomy or stenting; peripheral artery disease with revascularization; electrocardiographic changes on a graded exercise test; a positive imaging study; ≥50% diameter stenosis of a coronary, carotid, or lower extremity artery; and abdominal aortic aneurysm ≥5 cm.[7] Data on the clinical primary end point and BP were collected for 1206±256 days.

Outcome

For this analysis, the first occurrence of stroke was considered as the primary clinical end point (CE). In SPRINT, stroke was diagnosed based on signs and symptoms and on computed tomography or magnetic resonance imaging of the brain and large vessels showing a new lesion. In the absence of a new lesion on imaging, clinical findings consistent with the occurrence of stroke that lasted more than 24 hours were required.

Data Source

The data for this manuscript were accessed from SPRINT_POP (Primary Outcome Paper) Research Materials obtained from the National Heart, Lung and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center (BIOLINCC). This analysis and report do not necessarily reflect the opinions or views of SPRINT_POP or the NHLBI. SPRINT_POP Research Materials are available by BIOLINCC upon reasonable request. The analysis received Medical University of Warsaw Ethics Committee approval. The SPRINT study was approved by the institutional review board at each participating study site. Informed consent was obtained from all participants.

Statistical Analysis

This is a retrospective analysis of SPRINT data. Student *t* tests and analysis of variance were employed for the comparison of ≥2 groups, respectively. The chi squared test was used to compare discrete variables. Univariate and multivariate Cox proportional hazard risk models were used to estimate stroke risk. A final multivariate Cox model was established after removing non-significant variables (P=0.05 was selected as the cut-off value). All Cox models were tested for assumption of proportional hazards using scaled Schoenfeld residuals.

We used Kaplan–Meier curves to present stroke-free survival with log-rank test comparison. The differences were considered significant at P<0.05. Continuous variables are presented as means and standard deviations. Discrete variables are expressed as percentages. All computations were performed using STATISTICA 13 (StatSoft, Tulsa, OK, USA) with code programmed in the R 3.4.0 environment for statistical computations.[20] Standard, "survival," and "survminer" packages were used.[21,22]

Results

Our study included 8944 patients (95.5% SPRINT participants)—3156 (35.3%) men and 5788 (64.7%) women. The patients were randomly allocated to standard (4463; 49.9%) or intensive treatment (4481; 50.1%). In the standard and intensive treatment arms, on-treatment SBP and DBP were, respectively, 135.1±7.5/75.1±9.4 mm Hg and 120±8.6/67.5±8.4 mm Hg (P<0.0001).

Descriptive statistics for the whole study population and comparison between stroke and non-stroke groups are presented in Table 1. Stroke occurred in 110 (1.2%) participants during the analyzed period: 61 in the standard treatment group and 49 in the intensive treatment group (55.5% versus 44.5%; P=0.24). During the first 6 months of the original trial, 22 strokes occurred; we have not included these in our analysis. The mean (within participants) of median (within individual participant visit) SBP values was 127.6 mm Hg; for DBP, it was 71.3 mm Hg. The prevalence of clinical cardiovascular disease, chronic kidney disease, and age ≥75 years were higher in participants with stroke than in those without it during the analyzed period (30% versus 16.5%, P<0.0002; 39.1% versus 28%, P=0.01; and 40% versus 27.7%, P=0.004, respectively).

A detailed comparison between participants with DBP <70 mm Hg and ≥70 mm Hg is presented in Table 2. In the whole study population, the first-stroke rate was higher with DBP <70 mm Hg (1.5% versus 1.0%, P=0.044). The standard treatment group had significantly higher stroke rates with DBP <70 mm Hg (corresponding to the lowest DBP quartile) compared with higher DBP (2.0% versus 1.1%, P=0.03). In the intensive treatment group, however, the stroke rate did not differ between participants with DBP <70 mm Hg and those with DBP ≥70 mm Hg (1.3% versus 0.9%, P=0.24).

Overall, the study participants with DBP <70 mm Hg had a higher incidence of clinical cardiovascular diseases and chronic kidney disease, respectively (22.1% versus 12.1%, P<0.0001; and 34.7% versus 23.3%, P<0.0001). These participants were also older (72.4±8.6 versus 64.6±8.5 years, P<0.0001). Despite lower SBP (123.6 versus 130.6 mm Hg, P<0.0001),

Table 1. Clinical Characteristics of the Group and Comparisons Between Those Who Had and Did Not Have a Stroke

Parameter	All Participants (n=8944)	Participants Who Met CE (n=110)	Remaining Participants (n=8834)
Allocation to intensive treatment arm (n, %)	4463 (49.9)	49 (44.5)	4432 (50.2)
On-treatment SBP, mm Hg	127.6±11.0	131.6±12.6	127.6±11.0
On-treatment DBP, mm Hg	71.3±9.7	70.3±11.1	71.3±9.7
On-treatment PP, mm Hg	56.4±11.2	61.5±12.0	56.4±11.2
Baseline SBP, mm Hg	139.7±15.6	144.2±16.1	139.6±15.6
Baseline DBP, mm Hg	78.1±11.9	76.6±13.3	78.1±11.9
Baseline PP, mm Hg	61.5±14.4	67.6±16.1	61.5±14.3
Women (n, %)	3156 (35.3)	39 (35.5)	3117 (35.3)
Age, y	67.9±9.4	71.7±9.9	67.8±9.4
Smoking status (non/former/ current smokers) (%)	44.1/42.7/13.1	44.5/40/15.5	44.0/42.7/13.1
Black (n, %)	2793 (31.2)	28 (25.5)	2765 (31.3)
BMI, kg/m^2	29.9±5.8	29.5±6.0	29.9±5.8
Clinical cardiovascular disease (n, %)	1491 (16.1)	33 (30.0)	1458 (16.5)
Chronic kidney disease (n, %)	2515 (28.1)	43 (39.1)	2472 (28)
Time of observation, d	1206.1±259.8	1177.7±314.7	1206.5±259.0
Time to event /censoring, d	1197.5±269.8	699.5±302.1	1203.7±263.5

BMI indicates body mass index; CE, clinical end point; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

Table 2. Characteristics of Participants With DBP <70 mm Hg and DBP ≥70 mm Hg

Parameter	Participants With DBP <70 mm Hg (n=3792)	Participants With DBP ≥70 mm Hg (n=5152)	*P* Value
Allocation to intensive treatment arm (n, %)	2604 (68.7)	1877 (36.4)	<0.0001
On-treatment SBP, mm Hg	123.6±10.6	130.6±10.3	<0.0001
On-treatment DBP, mm Hg	62.3±5.3	77.9±6.2	<0.0001
On-treatment PP, mm Hg	61.3±11.5	52.8±9.5	<0.0001
Baseline SBP, mm Hg	139.9±15.5	139.6±15.6	0.1625
Baseline DBP, mm Hg	71.6±10.4	83.1±10.5	<0.0001
Baseline PP, mm Hg	68.3±14.2	56.3±12.0	<0.0001
Women (n, %)	1377 (36.3)	1779 (34.5)	0.08
Age, y	72.4±8.6	64.6±8.5	<0.0001
Smoking status (non/former/ current smokers) (%)	43.3/47.7//9	44.6/39.2/16.2	<0.0001
Clinical cardiovascular disease (n, %)	839 (22.1)	652 (12.7)	<0.0001
Chronic kidney disease (n, %)	1315 (34.7)	1200 (23.3)	<0.0001
Time of observation, d	1205.5±257.6	1206.6±261.4	0.85
Time to event/ censoring, d	1194.8±269.1	1199.6±270.3	0.404

DBP indicates diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

participants with DBP <70 mm Hg had higher pulse pressure (61.3 versus 52.8 mm Hg, *P*<0.0001).

DBP <70 mm Hg was related to higher stroke risk (hazard ratio [HR], 1.47; 95% CI, 1.01–2.13; *P*=0.0445) (Figure 2). Univariate proportional hazard Cox risk models revealed that age (HR, 1.05; 95% CI, 1.03–1.07; *P*<0.001), history of clinical cardiovascular disease (HR, 2.21; 95% CI, 1.47–3.33; *P*=0.001), history of chronic kidney disease (HR, 1.66; 95% CI, 1.13–2.43; *P*=0.010), and on-treatment SBP (HR, 1.03; 95% CI, 1.02–1.05; *P*<0.001) significantly affected stroke risk.

In accordance with other studies, we evaluated multivariate proportional hazard risk models beyond available parameters and on-treatment DBP to assess the impact on stroke risk of low on-treatment DBP.[23–25] Multivariate proportional hazard risk models beyond age, clinical cardiovascular disease, chronic kidney disease, current smoking status, on-treatment SBP, and on-treatment DBP (included as continuous variable or as dichotomous parameter using the cut-off of 70 mm Hg) are presented in Table 3. The application of these models revealed that only age, history of clinical

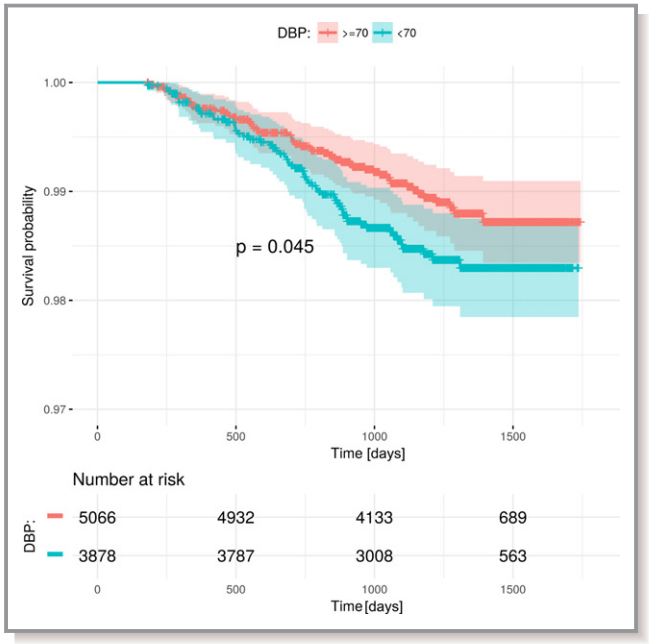

Figure 2. Kaplan–Meier plot of stroke-free survival in participants with diastolic blood pressure (DBP) <70 and ≥70 mm Hg. *P* value computed for comparison between Kaplan–Meier curves.

cardiovascular disease, current smoking status, and on-treatment SBP were significant. Baseline SBP and DBP were not significant factors after being entered into any of the models.

Figure 3 presents unadjusted and adjusted HRs in both treatment arms according to DBP quartile. Table 4 provides a detailed comparison within quartiles of DBP in both treatment arms.

Discussion

The main finding of the present study is that in the standard treatment group in participants with DBP <70 mm Hg, the rate of the first stroke was higher than for those with DBP ≥70 mm Hg (2.0% versus 1.1%, *P*=0.03). Similar relationship in the stroke rate was found in all investigated subjects with DBP <70 mm Hg ie, in both intensive and standard treatment groups (1.5% versus 1.0%, *P*=0.044). In contrast, the participants in the intensive-target group did not differ in stroke rates with DBP <70 mm Hg and DBP ≥70 mm Hg (1.3% versus 0.9%, *P*=0.24, respectively). We suggest that the similar stroke rate between these 2 subgroups having intensive treatment traces to a reduced stroke risk from the lower SBP compared with the standard arm (120.2±8.6 versus 135.1±7.5 mm Hg, *P*<0.0001). The participants with stroke had higher SBP and pulse pressure (131.6±12.6 versus 127.6±11.0 mm Hg, *P*=0.001; and 61.5±12.0 versus 56.4±11.2 mm Hg, *P*<0.0001; respectively).

Table 3. Multivariate Cox Proportional Hazard Risk Models for Stroke

Parameter	Hazard risk (95% CI)	*P* Value
Model A		
Age, y	1.04 (1.02–1.06)	<0.001
History of clinical cardiovascular disease	1.92 (1.32–3.00)	0.002
Current smoking status	1.78 (1.03–3.10)	0.04
On-treatment SBP, mm Hg	1.03 (1.01–1.05)	<0.001
Model B		
Age, y	1.04 (1.02–1.07)	0.001
History of clinical cardiovascular disease	1.87 (1.24–2.84)	0.003
Current smoking status	1.76 (1.01–3.05)	0.046
On-treatment DBP <70 mm Hg	1.30 (0.84–2.02)	0.242
On-treatment SBP, mm Hg	1.03 (1.02–1.05)	<0.001
Model C		
Age, y	1.05 (1.02–1.07)	0.001
History of clinical cardiovascular disease	1.93 (1.27–2.92)	0.002
Current smoking status	1.78 (1.03–3.1)	0.04
On-treatment DBP, mm Hg	1.00 (0.98–1.03)	0.96
On-treatment SBP, mm Hg	1.03 (1.01–1.05)	0.002
Model D		
Age, y	1.05 (1.03–1.09)	<0.001
History of clinical cardiovascular disease	1.97 (1.3–2.99)	0.001
Current smoking status	1.84 (1.06–3.2)	0.03
On-treatment DBP, mm Hg	1.02 (0.99–1.04)	0.197
Allocation to intensive treatment arm	0.89 (0.58–1.35)	0.574
Model E		
Age, y	1.05 (1.02–1.07)	0.001
History of clinical cardiovascular disease	1.92 (1.26–2.93)	0.002
Current smoking status	1.79 (1.02–3.1)	0.04
On-treatment DBP, mm Hg	1.00 (0.98–1.03)	0.962
On-treatment SBP, mm Hg	1.04 (1.02–1.06)	0.002
Female sex	0.98 (0.66–1.46)	0.93

DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

The existence of a J-curve phenomenon reflecting an adverse relationship between excessive BP reduction and cardiovascular risk is widely debated. SPRINT results showed beneficial and safe effects of SBP reduction, and these data have strongly influenced the newest US guidelines on hypertension management in adults.[7,26] SPRINT revealed that

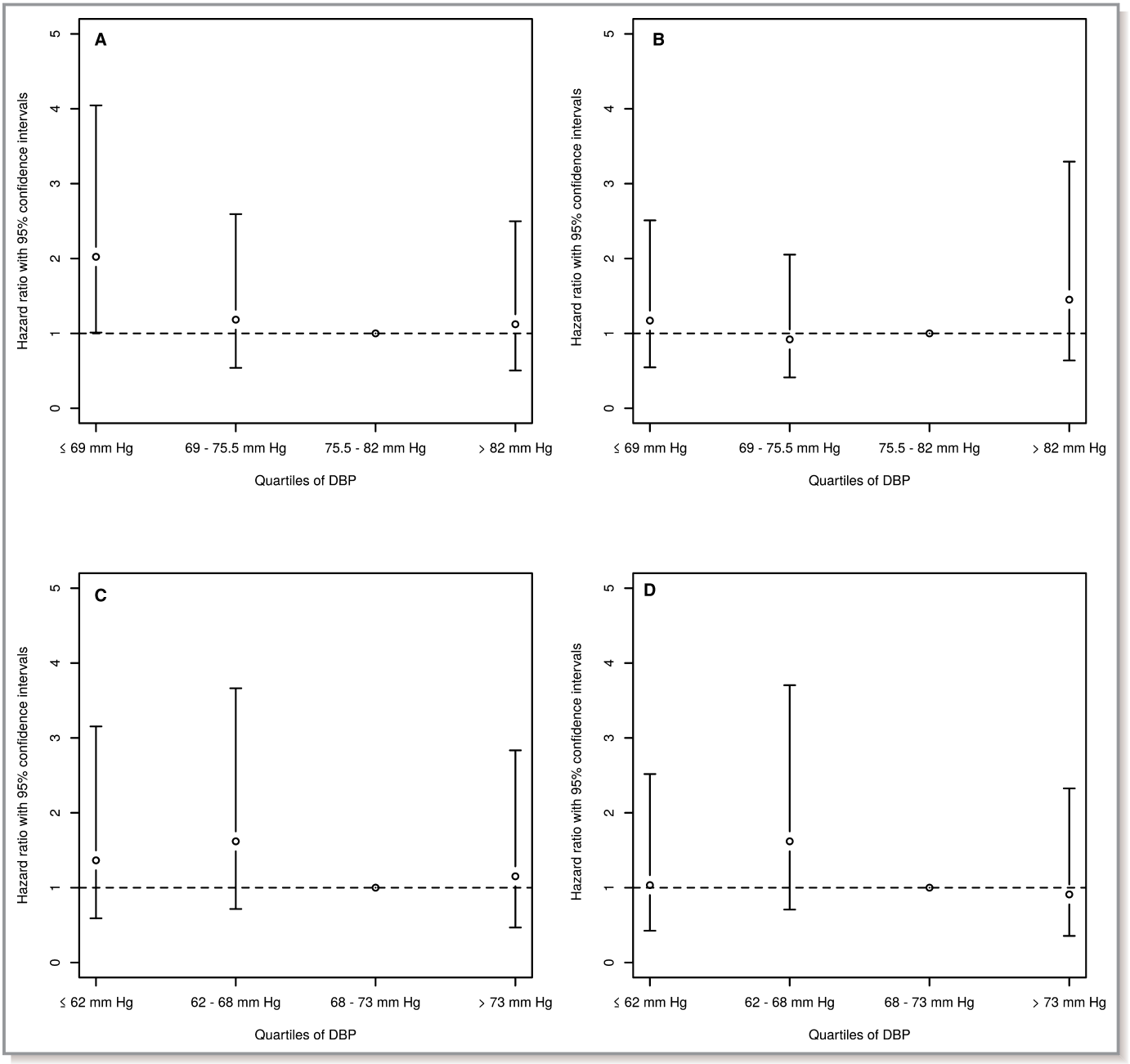

Figure 3. Plots of hazard ratios (HRs) with 95% CIs in quartiles of diastolic blood pressure (DBP) in standard and intensive treatment arms. HRs were computed in relation to the third quartile of DBP in each treatment arm. Adjustment of HR was performed as defined in a multivariate proportional hazard risk model. **A** and **B**, unadjusted and adjusted HRs in the standard treatment arm, respectively; **C** and **D**, unadjusted and adjusted HRs in the intensive treatment arm, respectively.

targeting SBP <120 mm Hg resulted in lower rates of its composite primary outcome; nevertheless, the analysis of its individual components showed that SBP decrease did not reduce the number of myocardial infarctions (HR, 0.83; 95% CI, 0.64–1.09, *P*=0.19) or strokes (HR, 0.89; 95% CI, 0.63–1.25; *P*=0.50).[7]

Several studies have addressed the influence of low DBP on cardiovascular events, but none has directly assessed the relationship between low DBP and stroke risk. A few post hoc analyses have been published based on SPRINT data, evaluating the effects of DBP lowering on cardiovascular risk. Beddhu et al showed an association of the lowest quintile of baseline DBP with an increased risk for the composite cardiovascular outcome in both intensive and standard therapy groups (59.5±6.9 and 65.0±7.6 mm Hg, respectively).[27] Stroke, however, was assessed as a part of the composite primary outcome and not as a separate end point. These authors indicated that a higher rate of cardiovascular episodes observed

Table 4. Comparison Within Quartiles of DBP in Both Treatment Arms

	Intensive Treatment Arm					Standard Treatment Arm				
	First Quartile (n=1211)	Second Quartile (n=1159)	Third Quartile (n=1056)	Fourth Quartile (n=1055)	*P* Value	First Quartile (N=1188)	Second Quartile (N=1073)	Third Quartile (N=1151)	Fourth Quartile (N=1051)	*P* Value
On-treatment SBP, mm Hg	119.3±8.3	118.6±7.4	119.9±7.9	123.3±10.1	<0.001	133.5±8.7	134.4±7.1	135.5±6.2	137.1±7.1	<0.001
On-treatment DBP, mm Hg	57.1±4.1	65.5±1.7	70.8±1.4	78.3±4.4	<0.001	63.1±4.9	72.6±1.8	78.9±1.9	86.9±3.7	<0.001
On-treatment PP, mm Hg	62.2±9.4	53.2±7.8	49.4±8	45.5±8.9	<0.001	70.1±9.8	61.8±7.4	56.5±6.5	50.2±6.8	<0.001
Baseline SBP, mm Hg	140.4±15.3	139.1±15.5	138.9±15.6	139.8±16.5	0.082	140.4±15.9	139±15.2	139.6±15.6	139.5±14.7	0.1923
Baseline DBP, mm Hg	68.4±9.5	77±9.2	81.7±9.5	87.2±10.4	<0.001	67.5±9	75.9±8.4	81.6±9.4	88.3±9.9	<0.001
Baseline PP, mm Hg	72±13.5	62.1±12	57.1±11.6	52.7±11.8	<0.001	72.8±14.3	63.1±11.7	57.9±11.2	51.2±9.8	<0.001
Women (n, %)	429 (35.4)	391 (33.7)	387 (36.6)	394 (37.3)	0.303	464 (39.1)	386 (36.0)	391 (34.0)	314 (29.9)	<0.001
Age, y	74.7±7.7	68.6±8.4	65.5±8.2	61.8±7.7	<0.001	74.9±7.7	69.7±8.5	65.3±7.8	60.8±7.1	<0.001
Smoking status (non/former/current smokers) (%)	43.4/49.6/7.0	42.9/44.1/12.9	46.8/40.2/13.0	42.9/34.8/22.3	<0.001	42.4/50.2/7.2	45.9/46.2/7.8	45.3/40.5/14.2	43.2/34.1/22.5	<0.001
Clinical cardiovascular disease (n, %)	295 (24.4)	201 (17.3)	137 (13.0)	115 (10.9)	<0.001	308 (25.9)	183 (17.1)	152 (13.2)	100 (9.5)	<0.001
Chronic kidney disease (n, %)	461 (38.1)	337 (29.1)	246 (23.3)	234 (22.2)	<0.001	464 (39.1)	306 (28.5)	257 (22.3)	210 (20.0)	<0.001
Time of observation, d	1210.1±254.8	1222.0±250.4	1216.1±258.4	1177.7±282.6	<0.001	1185.9±262.8	1210.1±257.0	1228.4±247.3	1197.2±262.1	<0.001
Time to event/censoring, d	1201.5±263.8	1213.1±263.6	1211.0±264.8	1171.4±289.8	<0.001	1171.2±277.6	1200.3±267.6	1220.9±256.9	1189.3±270.5	<0.001

DBP indicates diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

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at lower levels of DBP was not a direct response to DBP reduction but rather the result of patients' clinical characteristics associated with low DBP. That inference is in line with our findings on stroke. In a multivariate hazard risk model, we found that age and a history of clinical cardiovascular disease significantly affected stroke risk.

Stensrud et al found that after adjustment for treatment, low DBP (<60 mm Hg) was associated with a poor primary outcome, including stroke (HR, 1.9; 95% CI, 1.46–2.47).[28] After adjustment for demographic and clinical covariates, however, HR values significantly improved (HR, 1.04; 95% CI, 0.98–1.10]). A further analysis confined to the participants over 75 years found no harmful effects of DBP <60 mm Hg on the primary outcome. The results of both studies showed that the effect of low DBP on the risk of the composite end point is removed following adjustment for confounding variables. Neither Beddhu et al nor Stensrud et al included a separate analysis for stroke risk.[27,28]

A limited number of trials have addressed the possibility of a J-shaped relationship between low DBP and stroke risk. Voko et al found that in elderly participants treated to DBP <65 mm Hg, stroke risk was clearly higher than with DBP 65 to 74 mm Hg. This finding supports the idea of the J-curve phenomenon.[11] In patients aged >60 years who participated in SHEP, those who were actively treated to DBP 68 mm Hg had a significantly lower relative risk of stroke (0.64, P=0.0003) compared with the placebo group with DBP 72 mm Hg.[14] In the ACCORD trial, which included patients with diabetes mellitus, DBP 64.4 mm Hg versus 70.5 mm Hg resulted in a significant reduction in all strokes and non-fatal strokes.[5] In another analysis, the participants in ACCORD who met the eligibility criteria for SPRINT intensive BP control had a significantly reduced risk of the main composite outcome. This outcome included stroke, with the trend to the reduction in non-fatal stroke risk.[29] A subsequent analysis evaluated intensive and standard BP control in ACCORD participants 4 years after its termination.[30] After >9 years of follow-up, similar to the previous study, intensive BP control reduced the risk for the composite primary outcome by 25% (HR, 0.75; 95% CI, 0.60–0.95; P=0.02); however, the risk for non-fatal stroke remained unchanged. The effects were observed despite similar BP achieved during observational follow-up. None of these studies directly reported DBP, but their results support the favorable effects of intensive BP reduction observed in the ACCORD study.

In contrast to the ACCORD study, the HOT trial showed no direct effect on stroke risk of DBP reductions to ≤90, ≤85, ≤80, or 70 mm Hg in the overall study population or in the subgroup of participants with diabetes mellitus.[4] Only the group with ischemic heart disease had a 43% stroke reduction with DBP ≤80 mm Hg compared with a ≤90 mm Hg target.

Vidal-Petiot et al analyzed patients with coronary artery disease in different ranges of systolic and diastolic BP[31] and found no effect on stroke risk of DBP <60 or 60 to 69 mm Hg compared with 70 to 79 mm Hg. These results seem to argue against a J-curve phenomenon. The study, however, was based on the population from routine medical practice with no predefined BP interventions, and the number of stroke episodes was smaller than the numbers for other investigated end points. McEvoy et al found similar outcomes in a cohort from the Atherosclerosis Risk in Communities study, investigating the association between DBP <60 mm Hg and cardiovascular end points including stroke.[32] Over a median follow-up of 21 years, DBP reduction to <60 mm Hg was associated with a higher risk of myocardial damage and mortality compared with DBP 80 to 89 mm Hg; however, the risk of stroke was not increased with the lower DBP (HR, 1.13; 95% CI, 0.79–1.61). These authors emphasized that the sensitivity analysis evaluating a SPRINT-eligible subpopulation was underpowered because of a small sample size.[32]

The diverse effects of DBP reductions on stroke risk and myocardial infarction are possibly related to physiological differences in regulation of cerebral and coronary blood flow. Coronary blood flow occurs predominantly during the diastolic phase of the cardiac cycle and depends mostly on heart rate and DBP differences between aorta and mean pressure in the right atrium. Consequently, anything that significantly decreases DBP or increases heart rate will decrease coronary blood flow and lead to heart muscle damage.[31] Cerebral blood flow in normotensive adults is preserved between about 60 and 160 mm Hg. In hypertension, however, these values can shift upward.[33] All BP fluctuations beyond the range of autoregulation mean that cerebral flow shows a linear dependence on mean BP.

Our analysis has got some limitations. Firstly, as it is necessary with a post hoc data analysis, the conclusions should be interpreted and applied with caution. Second, SPRINT was stopped prematurely, after a median follow-up of 3.26 years; a longer follow-up could substantially have increased the number of strokes and altered these final results. Also it is worth noting that SPRINT did not include the participants with previous stroke, diabetes mellitus, or lower cardiovascular risk, so these results do not reflect potential effects in these subpopulations.

Some concerns have been raised about the specific BP measurement method in SPRINT. During the study, 3 unattended BP recordings were made after a 5-minute period of rest and then averaged. It was noted that the automated method of BP measurement might not correspond to the routine clinic BP practices because of the elimination of patient- and clinician-related factors. Agarwal found that 3 averaged measurements called "research-grade" SBP/DBP were lower by 12.7/12 mm Hg than routine clinic

measurements.[34] Filipovsky et al indicated differences between automated and office SBP/DBP recordings (15.0±13.8/8.0±7.3 mm Hg, respectively), with even lower automated than home BP recordings.[35] These observations suggest that BP values achieved in SPRINT were considerably higher than the intended goals of the therapy. One may assume that, the cut point in our study for the lowest range of DBP should be increased to 70 to 80 mm Hg. However, the recent survey results showed that both BP and risk reduction were similar in the intensive SPRINT group regardless of the method.[36]

The choice of median as a parameter to describe BP in our study requires explanation. Similar published reanalyses have used means covering the entire trial period.[37,38] In our opinion, median is a better central tendency parameter to characterize DBP and SBP because of the strategy used to achieve BP goals and the lower susceptibility of medians to outlier measurements. We performed additional analyses and concluded that the choice of median or mean did not affect our conclusions (data not shown).

Conclusion

In summary, our results indicate that in a high-risk SPRINT population with low DBP (<70 mm Hg), stroke risk was increased only if the participants were older, had a history of clinical cardiovascular disease, were smokers, or had a high SBP. We emphasize that the current study searches for causal relationship between low DBP and the risk of stroke. What we found was that apart from DBP, other clinical variables play significant roles. Therefore, DBP does not appear to be useful for prediction purposes.

Our findings strongly support the idea that BP goals should be tailored to a patient's individual characteristics. In each case, the patient's clinical profile should be carefully evaluated. Further studies are needed to resolve the association of low DBP and stroke risk in some subpopulations, including those with the history of stroke. Ongoing studies (such as the Optimal Blood Pressure and Cholesterol Targets for Preventing Recurrent Stroke in Hypertensives trial) should yield new data and help to generate appropriate recommendations.[39]

Disclosures

None.

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