












ORIGINAL RESEARCH

Intensive Blood Pressure Lowering in Individuals With Low Diastolic Blood Pressure and Elevated Troponin Levels in SPRINT

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BACKGROUND: Among individuals with hypertension and low diastolic blood pressure (DBP), the optimal BP target remains controversial due to concerns that BP lowering may reduce coronary perfusion. We determined the impact of intensive BP control among individuals with elevated systolic BP who have low DBP and elevated hs-cTnT (high-sensitivity cardiac troponin T) levels.

METHODS AND RESULTS: A total of 8828 participants in SPRINT (Systolic Blood Pressure Intervention Trial) were stratified by baseline DBP. Those with low DBP (<70 mm Hg) were further stratified by elevated hs-cTnT (≥ 14 ng/L) at baseline. The effects of intensive versus standard BP lowering on a cardiovascular disease composite end point, all-cause death, and 1-year change in hs-cTnT were determined. The combination of low DBP/high hs-cTnT was independently associated with a higher risk for cardiovascular disease and all-cause death, as well as greater 1-year increases in hs-cTnT, compared with DBP ≥ 70 mm Hg. However, randomization to intensive versus standard BP lowering led to similar reductions in cardiovascular disease risk among individuals with low DBP/high hs-cTnT (hazard ratio [HR], 0.82 [95% CI, 0.57–1.19]), low DBP/low hs-cTnT (HR, 0.48 [95% CI, 0.29–0.79]), and DBP ≥ 70 mm Hg (HR, 0.73 [95% CI, 0.60–0.89]; *P* for interaction=0.20). Intensive BP lowering also led to a reduction in all-cause death that was similar across groups (*P* for interaction=0.57).

CONCLUSIONS: In this nonprespecified subgroup analysis of SPRINT, individuals with low DBP and elevated hs-cTnT, low DBP and nonelevated hs-cTnT, and DBP ≥ 70 mm Hg derived similar cardiovascular disease and mortality benefits from intensive BP lowering. These findings warrant confirmation in other studies.

Key Words: diastolic blood pressure ■ hypertension ■ J curve ■ SPRINT ■ troponin

Hypertension affects nearly half of all US adults and is the leading modifiable contributor to cardiovascular disease (CVD) and early death.^{1,2} Among nondiabetic individuals with hypertension and at high CVD risk, the SPRINT trial (Systolic Blood Pressure Intervention Trial) demonstrated that targeting a systolic

blood pressure (SBP) of <120 mm Hg versus <140 mm Hg significantly reduced CVD events and all-cause death.³ The findings from SPRINT led to practice guidelines recommending lower BP targets for hypertension treatment, but controversy remains regarding the optimal BP target when low diastolic blood pressure (DBP)

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CLINICAL PERSPECTIVE

What Is New?

- In SPRINT (Systolic Blood Pressure Intervention Trial), the baseline combination of low diastolic blood pressure (DBP) and elevated levels of hs-cTnT (high-sensitivity cardiac troponin T), a marker of myocardial injury, was associated with greater risk of cardiovascular disease and death compared with those without low baseline DBP, whereas those with low DBP and nonelevated hs-cTnT levels did not experience greater risk.
- Randomization to intensive-treatment (targeting systolic blood pressure <120mmHg) versus standard-treatment (targeting systolic blood pressure <140mmHg) led to similar decreases in cardiovascular disease and death and similar minor increases in hs-cTnT across groups.

What Are the Clinical Implications?

- Among individuals with hypertension and low DBP, the presence of elevated hs-cTnT levels identifies a high-risk group that may account for the J-curve relationship between DBP and cardiovascular disease risk.
- The findings from the present analysis reinforce the concept that low DBP does not have a directly causal relationship with cardiovascular disease and death.
- Low DBP should not be a barrier to intensive blood pressure management among SPRINT-eligible individuals.

Nonstandard Abbreviations and Acronyms

| | |
|---------------|--|
| PP | pulse pressure |
| SPRINT | Systolic Blood Pressure Intervention Trial |

is present.⁴ Previous observational studies demonstrate a J-shaped relationship between DBP and myocardial infarction, fatal and nonfatal CVD, and all-cause death.^{5–10} This has been hypothesized to result from reduced coronary perfusion. However, recent ancillary analyses of several large BP target trials observed that the benefits of intensive versus standard BP lowering are similar regardless of baseline DBP,^{11–16} and Mendelian randomization studies show no evidence of a J-curve relationship between genetically predicted DBP and CVD risk.^{17,18} These results indicate that the J-curve phenomenon likely instead represents confounding from factors that are related both to the

presence of low DBP and CVD risk, such as arterial stiffness or coronary atherosclerosis.

To our knowledge, prior analyses from BP target trials have not used an intermediary marker of myocardial damage to identify a subset of individuals with low DBP who may be particularly susceptible to the consequences of reduced coronary perfusion from additional BP lowering. Minimal elevations in hs-cTnT (high-sensitivity cardiac troponin T) levels, a marker of chronic myocardial injury, are common in the ambulatory setting and strongly associated with CVD and all-cause death.^{19–24} In addition, increases in hs-cTnT over time are associated with increased CVD risk.²⁵ Low DBP is strongly associated with elevated hs-cTnT levels, and individuals with both low DBP and elevated hs-cTnT are at substantially elevated CVD risk.^{26,27} Evaluating the effects of intensive BP lowering in those with low DBP and elevated hs-cTnT levels may help to reconcile the clinical importance and biological mechanisms of the J-curve, which could have implications for hypertension management.

Our objectives were (1) to evaluate in SPRINT the associations of low DBP and elevated hs-cTnT levels at baseline with CVD, all-cause death, and changes in hs-cTnT over time; (2) to determine whether the effects of intensive BP lowering on CVD, all-cause death, and changes in hs-cTnT varied among individuals with low DBP and elevated hs-cTnT levels, low DBP and nonelevated hs-cTnT levels, and those without low DBP. We hypothesized that compared with SPRINT participants without low DBP at baseline and participants with low DBP and nonelevated hs-cTnT levels, those with low DBP and elevated hs-cTnT levels would (1) be at greater risk for CVD and all-cause death and have greater increases in hs-cTnT over time and (2) derive similar relative CVD and mortality benefits from intensive BP lowering.

METHODS

Study Design

The design and protocol of SPRINT have been reported previously.^{3,28} In brief, SPRINT was a National Institutes of Health-funded open-label clinical trial that randomized participants with hypertension and at elevated CVD risk to an intensive SBP target of <120mmHg versus a standard SBP target of <140mmHg, with individual patient management at the discretion of the trial investigators. A total of 9361 participants were enrolled in SPRINT between November 2010 and March 2013 across 102 sites in the United States and Puerto Rico. Inclusion criteria were age ≥50 years; systolic BP 130–180mmHg; and high CVD risk (defined as prior clinical or subclinical CVD other than stroke, chronic kidney disease [estimated glomerular filtration rate

(eGFR) 20–59 mL/min per 1.73 m²], age ≥75 years, or 10-year CVD risk >15% based on the Framingham risk score). Key exclusion criteria included diabetes, prior stroke or transient ischemic attack, eGFR <20 mL/min per 1.73 m², symptomatic heart failure, or a left ventricular ejection fraction <35%. The SPRINT protocol comprised a baseline visit and follow-up visits monthly for the first 3 months and every 3 months thereafter. The trial was stopped early on the recommendation of the Data and Safety Monitoring Board, which noted substantive evidence of treatment benefit during their regular scheduled interim evaluation of the data. The SPRINT study was approved by the institutional review board at each participating study site, and all participants provided written informed consent.

This analysis was approved by the committees on human research at the University of California, Davis, the University of California, San Francisco, and the San Francisco Veterans Affairs HealthCare System. The data that support the findings of this study are available from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repositories and the corresponding author upon request.

BP and hs-cTnT Measurement

Baseline and follow-up BPs were recorded by trained study coordinators using an automated oscillometric measurement system (model 907XL, Omron Healthcare) during clinic visits after participants were seated for 5 minutes. The recorded BP was the mean of 3 BP readings taken 1 minute apart, as previously described.²⁹ Pulse pressure (PP) for each participant was calculated as SBP minus DBP.

Blood samples used for hs-cTnT measurement were obtained at the time of study entry and at the 12-month study visit, processed immediately, and stored at –80°C until measurements were performed at the SPRINT Central Laboratory (University of Minnesota, Minneapolis, MN). The hs-cTnT was measured from freshly thawed samples using an electrochemiluminescence immunoassay on the Roche Cobas 6000 platform (Roche Diagnostics, Indianapolis, IN) as previously described.³⁰ The hs-cTnT assay (5th generation) has an interassay coefficient of variation of 3.4% at 28.3 ng/L and 2.3% at 2076 ng/L, with a lower limit of quantitation of 6 ng/L.

Combined DBP and hs-cTnT Groups

Consistent with previous studies in SPRINT, low DBP was defined as <70 mmHg and elevated hs-cTnT was defined as ≥14 ng/L.^{30–32} Participants were categorized at baseline as low DBP with elevated hs-cTnT (low DBP/high hs-cTnT), low DBP with non-elevated hs-cTnT (low DBP/low hs-cTnT), and DBP ≥70 mmHg, because the beneficial treatment effects of intensive

BP lowering are established among those with normal and high DBP.¹³

Outcomes

The primary outcome of this ancillary analysis was SPRINT's CVD composite end point, which included nonfatal myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, acute decompensated heart failure, stroke, and death from CVD. As previously described, SPRINT outcomes were defined, ascertained, and formally adjudicated by a central committee of investigators blinded to treatment assignment.^{3,28} Secondary clinical outcomes included all-cause death and 1-year change in hs-cTnT.

Covariates

Age, sex, race, ethnicity, medical history, medications, and smoking status were obtained by questionnaire. Body mass index was calculated as weight in kilograms divided by height in meters squared. Fasting serum low-density lipoprotein cholesterol, serum creatinine, and urine albumin and creatinine were measured at the SPRINT Central Laboratory. The eGFR was calculated according to the 2021 Chronic Kidney Disease-Epidemiology Collaboration creatinine estimating equation without race.³³

Statistical Analysis

We evaluated the associations of baseline DBP/hs-cTnT categories with risk of the CVD composite outcome and all-cause death using multivariable Cox proportional hazards models. Models were adjusted for demographics (age, sex, race), treatment assignment, and baseline clinical characteristics (body mass index, smoking status, prevalent CVD, eGFR, urine albumin-to-creatinine ratio, low-density lipoprotein cholesterol, SBP, and statin use).

Event proportions were then compared between the intensive and standard SBP treatment arms among participants with low DBP/low hs-cTnT, low DBP/high hs-cTnT, and DBP ≥70 mmHg. Cox proportional hazards models were used to evaluate the effect of intensive versus standard BP lowering on the CVD composite outcome and all-cause death stratified by these groups. CIs were calculated using robust variance estimators. There was no evidence that the proportional hazards assumption for each outcome was violated in tests using Schoenfeld residuals. Variation of the treatment effect across groups for each outcome was assessed using a Wald test for multiplicative interaction terms in models that included main effects.

For analyses with change in hs-cTnT as the outcome, linear regression models were constructed with change in hs-cTnT defined as log(year 1 hs-cTnT)

minus $\log(\text{baseline hs-cTnT})$. Because 21% of hs-cTnT levels were below the limit of detection, we imputed undetectable values using a Tobit regression model.³⁴ Geometric mean ratios and 95% CIs were estimated. These models were additionally adjusted for the baseline hs-cTnT level.

In sensitivity analyses, we used multivariable Fine–Gray subdistribution hazard regression models to account for the competing risk of death (data not shown).³⁵ We also evaluated the effects of intensive versus standard BP lowering on the CVD composite outcome and all-cause death using a widened baseline PP (>70 mmHg) instead of low DBP; using prevalent CVD instead of baseline hs-cTnT level; and using a nonstroke CVD composite outcome because low DBP is associated with adverse CVD outcomes and death but not stroke.^{6,7,10}

All analyses were conducted using Stata software, version 17 (StataCorp LP, College Station, TX).

RESULTS

Study Population and Baseline Characteristics

Of the 9361 SPRINT participants, 8828 (94.3%) had baseline hs-cTnT measurements. In this study sample, 6757 (74.5%) had a baseline DBP ≥ 70 mmHg, 1287 (14.6%) had low DBP and nonelevated hs-cTnT levels, and 784 (8.9%) had low DBP and elevated hs-cTnT

levels. Mean baseline DBP in the DBP ≥ 70 mmHg, low DBP/low hs-cTnT, and low DBP/high hs-cTnT groups were 83, 63, and 62 mmHg, respectively, and median hs-cTnT levels were 8.8, 8.7, and 19.9 ng/L, respectively. Compared with the DBP ≥ 70 mmHg group, those with low DBP/high hs-cTnT were on average older, more often male, less often Black or Hispanic, less often current smokers, more likely to be on a statin, and had a higher PP and lower eGFR. Similarly, those with low DBP/low hs-cTnT were less often Black or current smokers, more likely to be on a statin, and had a higher PP; however, they were more likely to be female or Hispanic, and their mean eGFR and age fell between the other 2 groups (Table 1).

Associations With CVD, All-Cause Death, and Change in hs-cTnT

The CVD composite outcome occurred in 5.9% of participants with DBP ≥ 70 mmHg, 5.5% with low DBP/low hs-cTnT, and 14.4% with low DBP/high hs-cTnT (Figure S1). In multivariable models, compared with the DBP ≥ 70 mmHg group, participants in the low DBP/high hs-cTnT group had a significantly increased risk for the CVD composite outcome, whereas those with low DBP/low hs-cTnT had numerically lower risk (Table 2). Deaths occurred in 3.4% of participants with DBP ≥ 70 mmHg, 3.4% with low DBP/low hs-cTnT, and 9.7% with low DBP/high hs-cTnT. In multivariable models, compared with the DBP ≥ 70 mmHg group,

Table 1. Baseline Characteristics of SPRINT Participants Stratified by Combined Baseline DBP and hs-cTnT Categories

| Baseline characteristic | DBP ≥ 70 mmHg (N=6757) | DBP < 70 mmHg+hs-cTnT < 14 ng/L (N=1287) | DBP < 70 mmHg+hs-cTnT ≥ 14 ng/L (N=784) |
|---|-----------------------------|--|--|
| Age, y | 66.1 \pm 9.0 | 72.1 \pm 8.0 | 77.5 \pm 7.7 |
| Female sex | 2396 (35%) | 646 (50%) | 208 (27%) |
| Black race | 2140 (32%) | 277 (22%) | 168 (21%) |
| Hispanic ethnicity | 718 (11%) | 168 (13%) | 58 (7%) |
| hs-cTnT, ng/L | 8.9 (6.2–13.1) | 8.7 (6.4–11.1) | 19.9 (16.2–27.1) |
| DBP, mmHg | 83 \pm 9.1 | 63 \pm 5.0 | 62 \pm 5.9 |
| Systolic BP, mmHg | 142 \pm 15.0 | 131 \pm 14.8 | 134 \pm 15.3 |
| Pulse pressure, mmHg | 59 \pm 13.4 | 67 \pm 14.9 | 72 \pm 15.7 |
| Intensive BP arm | 3377 (50%) | 635 (49%) | 405 (52%) |
| Current smoker | 996 (15%) | 106 (8%) | 46 (6%) |
| Body mass index, kg/m ² | 30.3 \pm 5.8 | 28.3 \pm 5.2 | 28.4 \pm 5.6 |
| Prevalent cardiovascular disease | 1154 (17%) | 332 (26%) | 266 (34%) |
| Low density lipoprotein cholesterol, mg/dL | 115 \pm 35 | 107 \pm 34 | 98 \pm 30 |
| Statin use | 2705 (40%) | 679 (53%) | 432 (56%) |
| Number of BP meds | 1.8 \pm 1.1 | 2.1 \pm 1.1 | 2.5 \pm 1.1 |
| Estimated glomerular filtration rate, mL/min per 1.73m ² | 75 \pm 19 | 72 \pm 18 | 58 \pm 19 |
| Urine albumin-to-creatinine ratio, mg/g | 9 (6v21) | 9 (6–17) | 15 (8–43) |

Data displayed as N (%), mean \pm SD, or median (interquartile range). BP indicates blood pressure; DBP, diastolic blood pressure; hs-cTnT, high-sensitivity cardiac troponin T; and SPRINT, Systolic Blood Pressure Intervention Trial.

Table 2. Multivariable-Adjusted Associations Between Baseline Combined DBP and hs-cTnT Categories and Risk of the CVD Composite End Point and All-Cause Death

| Outcome | No. of events/total (%) | Model 1* HR (95% CI) | Model 2† HR (95% CI) |
|----------------------------------|-------------------------|----------------------|----------------------|
| CVD composite | | | |
| DBP ≥70 mm Hg | 399/6757 (5.9%) | Reference | Reference |
| DBP <70 mm Hg + hs-cTnT <14 ng/L | 71/1287 (5.5%) | 0.94 (0.73–1.21) | 0.79 (0.60–1.03) |
| DBP <70 mm Hg + hs-cTnT ≥14 ng/L | 113/784 (14.4%) | 2.74 (2.22–3.38) | 1.45 (1.13–1.87)‡ |
| All-cause death | | | |
| DBP ≥70 mm Hg | 231/6757 (3.4%) | Reference | Reference |
| DBP <70 mm Hg + hs-cTnT <14 ng/L | 44/1287 (3.4%) | 1.01 (0.73–1.39) | 0.87 (0.61–1.25) |
| DBP <70 mm Hg + hs-cTnT ≥14 ng/L | 76/784 (9.7%) | 3.08 (2.37–3.99) | 1.33 (0.96–1.84)‡ |

CVD composite end point includes myocardial infarction, acute coronary syndrome, heart failure, stroke, and cardiovascular death. CVD indicates cardiovascular disease; DBP, diastolic blood pressure; HR, hazard ratio; and hs-cTnT, high-sensitivity cardiac troponin T.

*Model 1 is unadjusted.

†Model 2 adjusts for baseline age, sex, race, treatment assignment, current smoking, prior CVD, body mass index, low-density lipoprotein cholesterol, statin use, systolic blood pressure, total number of antihypertensive medications, and estimated glomerular filtration rate.

‡Comparing those with DBP <70 mmHg and hs-cTnT <14 ng/L (referent group) vs those with DBP <70 mmHg and hs-cTnT ≥14 ng/L, the adjusted HR=1.96 (95% CI, 1.39–2.78) for the CVD composite outcome and the adjusted HR=1.82 (95% CI, 1.18–2.81) for all-cause death.

participants in the low DBP/high hs-cTnT group had a numerically higher risk of death, whereas the low DBP/low hs-cTnT group were at similar risk (Table 2).

There were 8027 (85.7%) SPRINT participants who also had hs-cTnT measured at year 1. In general, there were only minimal increases in hs-cTnT levels from baseline to year 1 across groups (Table 3). In multivariable models, compared with the DBP ≥70 mmHg group, the low DBP/high hs-cTnT had a 5% greater 1-year increase in hs-cTnT levels, whereas the low DBP/low hs-cTnT group had similar 1-year changes in hs-cTnT (Table 3).

Effects of Intensive BP Lowering on Change in SBP, DBP, and hs-cTnT

The distribution of achieved SBP at year 1 in the standard BP control arm (SBP target <140 mmHg) was similar across the DBP ≥70 mmHg, low DBP/low hs-cTnT, and low DBP/high hs-cTnT groups (Figure 1). A similar pattern was observed for the intensive BP control arm (SBP target <120 mmHg). The mean DBP at year 1 was 79, 68, and 66 mmHg in the standard BP

control arm of the DBP ≥70 mmHg, low DBP/low hs-cTnT, and low DBP/high hs-cTnT groups, respectively, and 71, 62, and 60 mmHg in the intensive BP control arm across the 3 groups, respectively. Median hs-cTnT levels at year 1 were similar in the DBP ≥70 mmHg and low DBP/low hs-cTnT groups in the standard and intensive BP control arms, whereas year 1 hs-cTnT levels were higher in the low DBP/high hs-cTnT group across both treatment arms (Figure 1).

Effects of Intensive BP Lowering on CVD and All-Cause Death

The effect of randomization to intensive versus standard BP lowering on the CVD composite outcome was similar among participants with low DBP/high hs-cTnT (hazard ratio [HR], 0.82 [95% CI, 0.57–1.19]) and those with DBP ≥70 mmHg (HR, 0.73 [95% CI, 0.60–0.89]), and although the effect appeared stronger among participants with low DBP/low hs-cTnT (HR, 0.48 [95% CI, 0.29–0.79]), the overall test for interaction across groups was not significant (P for interaction=0.21; Figure 2). Intensive BP lowering also led to a similar

Table 3. Multivariable-Adjusted Associations Between Baseline Combined DBP and hs-cTnT Categories and 1-Year Change in hs-cTnT

| Baseline DBP category | hs-cTnT level, ng/L | | 1-y Change in hs-cTnT | |
|----------------------------------|------------------------|----------------------|-----------------------|-----------------------|
| | Baseline, median (IQR) | Year 1, median (IQR) | Model 1* GMR (95% CI) | Model 2† GMR (95% CI) |
| DBP ≥70 mm Hg | 8.9 (6.2–13.1) | 8.9 (6.2–13.4) | Reference | Reference |
| DBP <70 mm Hg + hs-cTnT <14 ng/L | 8.7 (6.4–11.1) | 8.8 (6.5–11.6) | 1.04 (1.02–1.06) | 1.01 (0.99–1.04) |
| DBP <70 mm Hg + hs-cTnT ≥14 ng/L | 19.9 (16.2–27.1) | 20.3 (16.3–28.1) | 1.07 (1.03–1.11) | 1.05 (1.01–1.09)‡ |

DBP indicates diastolic blood pressure; GMR, geometric mean ratio; hs-cTnT, high sensitivity cardiac troponin T; and IQR, interquartile range.

*Model 1 adjusts for baseline log(hs-cTnT).

†Model 2 adjusts for model 1+baseline age, sex, race, treatment assignment, current smoking, prior cardiovascular disease, body mass index, low-density lipoprotein cholesterol, statin use, systolic blood pressure, total number of antihypertensive medications, and estimated glomerular filtration rate.

‡Adjusted GMR, 1.11 (95% CI, 0.92–1.33) comparing those with DBP <70 mmHg and hs-cTnT <14 ng/L vs those with DBP <70 mmHg and hs-cTnT ≥14 ng/L.

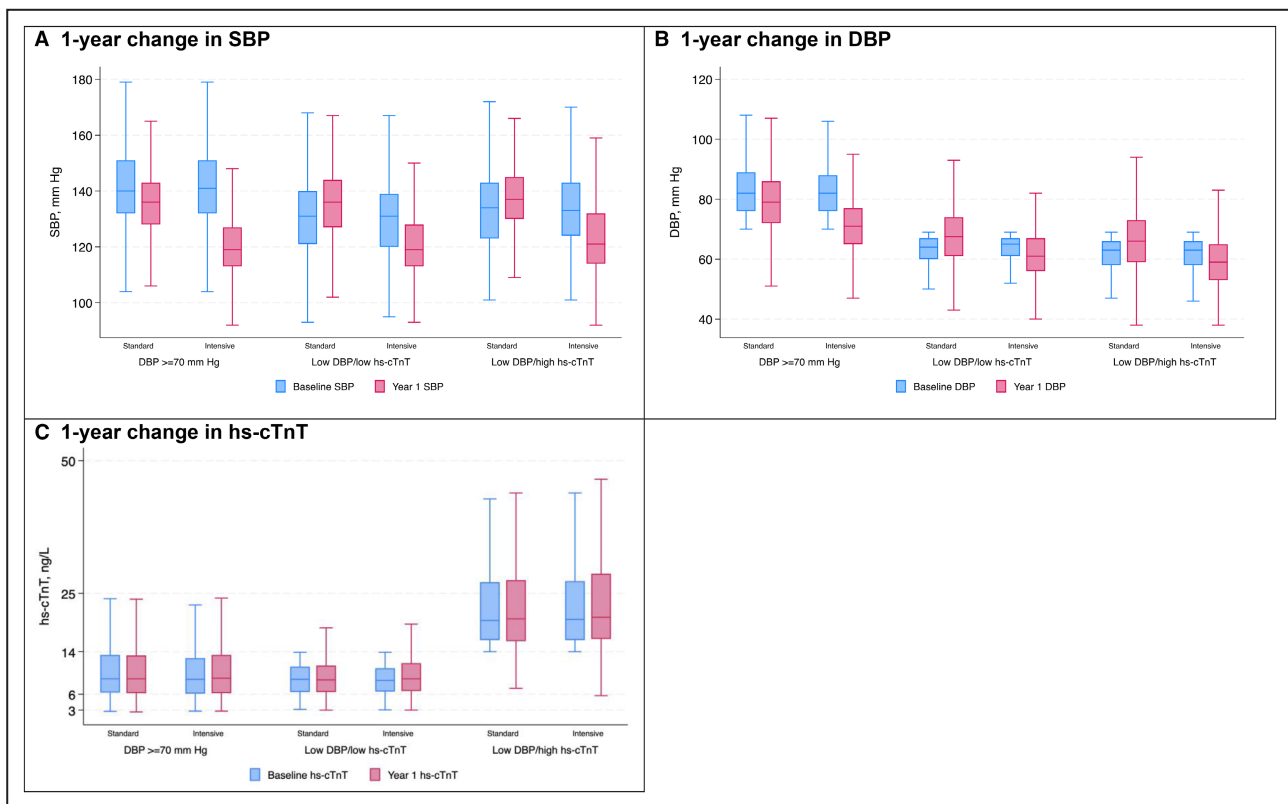


Figure 1. One-year changes in SBP, DBP, and hs-cTnT stratified by randomized treatment assignment and combined DBP and hs-cTnT categories.

The boxplots display the median as well as 25th and 75th percentiles of patients' mean measurements in the standard and intensive treatment arms at baseline (blue) and 1-year (red) for SBP (A), DBP (B), and hs-cTnT (C) by baseline DBP/hs-cTnT category. DBP indicates diastolic blood pressure; hs-cTnT, high sensitivity cardiac troponin T; and SBP, systolic blood pressure.

reduction in all-cause death among participants with low DBP/high hs-cTnT (HR, 0.83 [95% CI, 0.53–1.30]), low DBP/low hs-cTnT (HR, 0.76 [95% CI, 0.42–1.39]), and DBP \geq 70 mmHg (HR, 0.65 [95% CI, 0.50–0.84], P for interaction=0.60; Figure 2). In addition, intensive BP lowering led to minor increases in hs-cTnT at 1 year that was similar across groups (P for interaction=0.51; Table S1).

In sensitivity analyses, results were similar when accounting for the competing risk of death using Fine–Gray subdistribution hazard regression models. A similar pattern of results was also observed categorizing participants by widened PP instead of low DBP and categorizing by prevalent CVD instead of elevated baseline hs-cTnT levels (Table S2). Results were also similar using a nonstroke CVD composite outcome (Figure S2).

DISCUSSION

In this ancillary analysis of SPRINT, participants with low DBP and elevated hs-cTnT levels at baseline had a higher risk of the CVD composite outcome

and all-cause death compared with those with DBP \geq 70 mmHg. They also had greater increases in hs-cTnT over time. However, randomization to intensive versus standard BP lowering led to similar reductions in the CVD composite outcome and all-cause death.

Previous studies demonstrate that low DBP is associated with elevations in hs-cTnT and that this combination is strongly associated with increased risk for CVD and death, as well as greater increases in hs-cTnT over time.^{26,27} We extend these findings to SPRINT and show in a large study sample that, compared with participants with DBP \geq 70 mmHg, those with low DBP and elevated hs-cTnT levels were at higher risk of CVD, and those with low DBP and nonelevated hs-cTnT levels were at lower risk. These findings suggest that hs-cTnT can identify a high-risk group that may account for the J-curve relationship between DBP and CVD risk.

The putative mechanism underlying the J-curve has been reduced coronary perfusion pressure from low DBP, but recent ancillary analyses from BP target trials show that individuals with low baseline DBP derive similar CVD benefits from more intensive BP lowering as those without low baseline DBP.^{11–13} These findings suggested that the J-curve is more likely explained

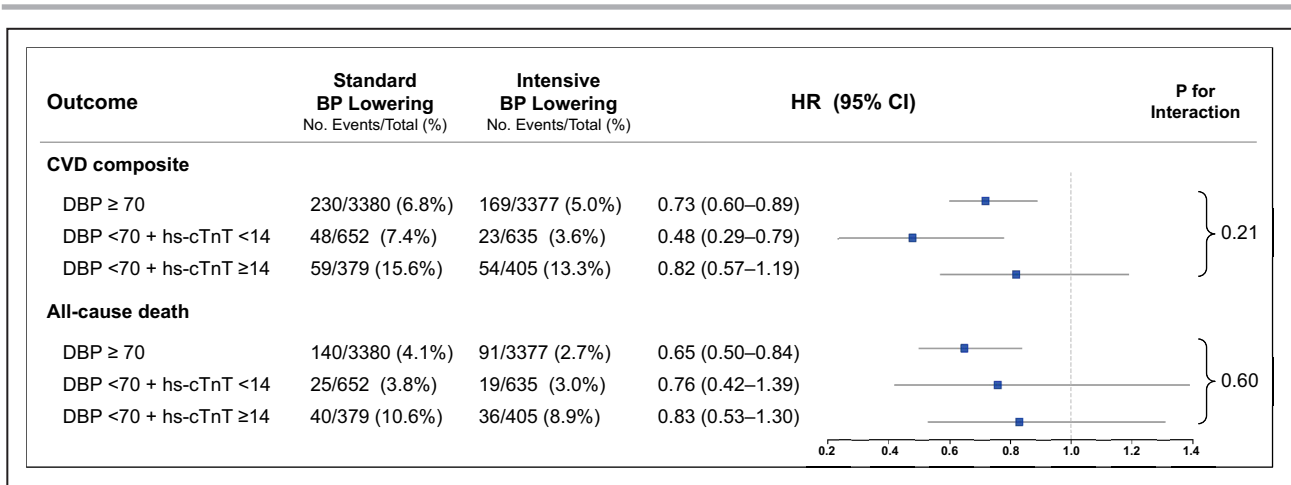


Figure 2. Effect of intensive BP lowering on the CVD composite end point and all-cause death stratified by baseline combined DBP and hs-cTnT categories.

The composite CVD outcome includes nonfatal myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, nonfatal acute decompensated heart failure, stroke, and death from CVD. HRs were obtained from multivariable Cox proportional hazards models that included age, sex, race, treatment assignment, current smoking, prior CVD, body mass index, low-density lipoprotein cholesterol, SBP, statin use, total number of antihypertensive medications, and estimated glomerular filtration rate. CVD indicates cardiovascular disease; DBP, diastolic blood pressure; HR, hazard ratio; hs-cTnT, high sensitivity cardiac troponin T; and SBP, systolic blood pressure.

by confounding or reverse causation. However, these studies lacked an intermediary marker of myocardial injury to better characterize those with low DBP. As an established marker of chronic myocardial injury, hs-cTnT would hypothetically be able to distinguish individuals with low DBP who are particularly susceptible to decreased coronary perfusion and consequently at higher risk of CVD events from additional BP lowering. The present study demonstrates for the first time in a randomized trial that intensive BP lowering among individuals with low DBP and elevated hs-cTnT levels leads to similar relative reductions in CVD and death and similar short-term changes in hs-cTnT, compared with individuals without low DBP and those with low DBP and nonelevated hs-cTnT levels. SPRINT participants with low DBP and nonelevated hs-cTnT levels appeared to have a stronger reduction in CVD risk with intensive BP lowering compared with the 2 other groups, although the overall test for interaction was not statistically significant. Taken together, these findings strengthen the evidence that low DBP does not have a directly causal relationship with CVD and death. This is reinforced by our sensitivity analyses using widened PP in place of low DBP and prevalent CVD in place of elevated hs-cTnT levels.

Our findings may be explained by the counterbalancing of possibly reduced coronary perfusion pressure with an improved overall myocardial oxygen supply-to-demand ratio. Given that myocardial oxygen usage improves as the systolic pressure–time index decreases, the effect of improved demand may outweigh the potential supply constraint that occurs with

decreased DBP.^{36,37} This is supported by our observation that intensive BP lowering did not lead to major differential increases in hs-cTnT in those with low DBP and elevated hs-cTnT levels at baseline. Although intensive BP lowering led to small increases in hs-cTnT across groups, recent work has shown that this is likely mediated by benign hemodynamic decreases in eGFR seen with intensive BP lowering.³⁸

The present study supports the use of lower BP targets in clinical practice, even among individuals with low DBP and evidence of subclinical myocardial injury or prevalent clinical CVD. Prior ancillary analyses of SPRINT and other BP target trials show that other potential harms of intensive BP lowering, including serious adverse events such as acute kidney injury, syncope, hypotension, and electrolyte abnormalities, are similar irrespective of baseline DBP.^{11–13} In addition, the effects of intensive BP lowering on cognitive outcomes and cerebral perfusion appear to be similar among SPRINT participants with or without low DBP.³⁹

Our analysis benefited from the use of randomized data to minimize the impact of confounding, rigorously adjudicated CVD and death outcomes, and repeated hs-cTnT measurements available in the majority of SPRINT participants. There were also several limitations. First, due to the relatively small proportion of participants with low DBP and elevated hs-cTnT at baseline, the similar effects of intensive BP lowering on CVD and mortality across groups may be a chance finding and should be interpreted as exploratory. Further research is required to confirm these results. Second, elevations in hs-cTnT may reflect multiple pathophysiologic

mechanisms of chronic myocardial injury that may not confer similar susceptibility to reduced coronary perfusion pressure from low DBP. Third, our findings may not be generalizable to low DBP outside the baseline range in SPRINT, or to individuals who would not meet the inclusion criteria for SPRINT, including those with diabetes or prior stroke and those who are younger in age or at lower CVD risk.

CONCLUSIONS

In summary, we demonstrated that even though individuals with low DBP and elevated hs-cTnT levels are at higher CVD and mortality risk and have greater increases in hs-cTnT over time compared with those without low DBP, the CVD and mortality benefits of intensive BP lowering are similar. These novel findings strengthen the evidence that low DBP is not directly causal of CVD risk and reinforces the concept that low DBP among individuals with hypertension should not be a barrier to intensive BP control.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S2

Figures S1–S2

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