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ORIGINAL RESEARCH

Associations of High-Sensitivity Troponin and Natriuretic Peptide Levels With Serious Adverse Events in SPRINT

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BACKGROUND: Assessing the risk of serious adverse events (SAEs) during hypertension treatment is important for understanding the benefit-harm trade-offs of lower blood pressure goals. It is unknown whether high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) provide information about SAEs.

METHODS AND RESULTS: In SPRINT (Systolic Blood Pressure Intervention Trial), hs-cTnT and NT-proBNP were measured at baseline in 8828 (94.3%) and 8836 (94.4%) participants, respectively. Multivariable Cox proportional hazards models were used to evaluate hs-cTnT and NT-proBNP associations with a composite of SPRINT's SAEs of interest: hypotension, syncope, bradycardia, acute kidney injury, electrolyte abnormalities, and injurious falls. Elevations in hs-cTnT and NT-proBNP were associated with increased composite SAE risk (hazard ratio [HR] per 2-fold higher hs-cTnT: 1.15; 95% CI, 1.06–1.25; HR per 2-fold higher NT-proBNP: 1.09; 95% CI, 1.05–1.14). Compared with both hs-cTnT and NT-proBNP in the lower tertiles, both biomarkers in the highest tertile was associated with increased composite SAE risk (HR, 1.56; 95% CI, 1.32–1.84). Composite SAE risk was higher in the intensive-treatment group than in the standard-treatment group for participants with both biomarkers in the lower tertiles, but similar between treatment groups for participants with both biomarkers in the highest tertile (*P* for interaction=0.008).

CONCLUSIONS: Elevations in hs-cTnT and NT-proBNP individually and in combination are associated with higher composite SAE risk in SPRINT. The differential impact of blood pressure treatment on SAE risk across combined biomarker categories may have implications for identifying individuals with more favorable benefit-harm profiles for intensive blood pressure lowering.

Key Words: adverse events ■ brain natriuretic peptide ■ hypertension ■ SPRINT ■ troponin

Elevated systolic blood pressure (BP) of 140 mm Hg or higher affects an estimated 874 million adults worldwide and is a leading contributor to cardiovascular disease (CVD), disability, and early death.[1,2] In non-diabetic individuals with hypertension and at high CVD risk, SPRINT (Systolic Blood Pressure Intervention Trial) demonstrated that targeting a systolic BP of <120 mm Hg compared with <140 mm Hg significantly reduced the risk of CVD and all-cause mortality.[3] These findings led to updated guidelines recommending lower BP targets based on BP levels and predicted CVD risk.[4,5] However, intensive BP lowering in SPRINT was also associated with an increased risk of several serious adverse events (SAEs), including hypotension, syncope, electrolyte abnormalities, and acute kidney injury (AKI).[3] While multiple modalities for CVD risk assessment have been studied, strategies for SAE risk assessment are not well-characterized.[6,7]

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CLINICAL PERSPECTIVE

What Is New?

- In SPRINT (Systolic Blood Pressure Intervention Trial), higher cardiac biomarker levels individually and in combination are associated with greater risk of serious adverse events.
- Serious adverse events were more common in the intensive-treatment group (targeting a systolic blood pressure <120 mm Hg) than in the standard-treatment group (targeting a systolic blood pressure <140 mm Hg) for participants with low cardiac biomarker levels, but were similar between treatment groups for participants with high cardiac biomarker levels.

What Are the Clinical Implications?

- Cardiac biomarkers provide prognostic information about risk of serious adverse events during hypertension treatment independent of clinical characteristics.
- Individuals with high cardiac biomarker levels do not appear to have an excess risk of serious adverse events from intensive blood pressure lowering compared with standard blood pressure lowering.
- Measuring cardiac biomarkers in the general population may be useful for hypertension treatment decisions.

Nonstandard Abbreviations and Acronyms

AKI	acute kidney injury
hs-cTnT	high-sensitivity cardiac troponin T
SPRINT	Systolic Blood Pressure Intervention Trial

Cardiac troponin T, a marker of myocardial cell injury that is measured with a highly sensitive assay (hs-cTnT), and N-terminal pro-B-type natriuretic peptide (NT-proBNP), a marker of neurohormonal stress, represent established biomarkers of CVD risk.[8–22] Recently, elevations in hs-cTnT and NT-proBNP have been shown to identify SPRINT participants who derive the greatest absolute benefit from intensive BP lowering.[23] Elevations in hs-cTnT and NT-proBNP in older adults are also associated with risk of falls, orthostatic hypotension, and hospitalizations with AKI.[24–26] However, it remains unknown whether cardiac biomarkers provide prognostic information about SAEs during hypertension treatment.

Our primary objective was to evaluate the associations of baseline concentrations of hs-cTnT and NT-proBNP with SAEs in SPRINT. We also evaluated whether these biomarkers modified the effect of randomized treatment assignment (intensive versus standard BP lowering) on SAE risk. We hypothesized that elevations in hs-cTnT and NT-proBNP would be associated with a higher risk of SAEs, independent of clinical characteristics, treatment assignment, and one another.

METHODS

Study Design

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. The design and protocol of SPRINT have been reported previously.[3,27] In brief, SPRINT was a National Institutes of Health-funded open-label clinical trial that randomized participants with hypertension to an "intensive" systolic BP target of <120 mm Hg versus a "standard" systolic BP target of <140 mm Hg, with individual patient management at the discretion of the trial investigators. Inclusion criteria were age ≥50 years; systolic BP 130–180 mm Hg; and high CVD risk (defined as prior clinical or subclinical CVD other than stroke, chronic kidney disease [eGFR 20–59 mL/min per 1.73 m^2], 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 m^2, symptomatic heart failure, or a left ventricular ejection fraction <35%. A total of 9361 participants were enrolled between November 2010 and March 2013 across 102 sites in the United States and Puerto Rico. The SPRINT protocol comprised a baseline visit and follow-up visits monthly for the first 3 months and every 3 months thereafter. The average difference in systolic BP between treatment groups was 14 mm Hg over the course of the trial. 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 ancillary study measured baseline concentrations of hs-cTnT and NT-proBNP in SPRINT participants, and was approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center, the University of California, San Francisco, the San Francisco Veterans Affairs Health Care System, and the Veterans Affairs San Diego Healthcare System.

Exposures

All samples were obtained at the time of study entry, processed immediately, and stored at −80°C until biomarker measurements were performed at the SPRINT Central Laboratory (University of Minnesota, Minneapolis, MN). Both hs-cTnT and NT-proBNP were measured from freshly thawed serum samples using an electrochemiluminescence immunoassay on the Roche Cobas 6000 platform (Roche Diagnostics, Indianapolis, IN) as previously described.[23] The hs-cTnT assay (5th Generation) has an imprecision 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. The NT-proBNP assay has an imprecision of 2.9% at 140.3 pg/mL and 2.7% at 4563 pg/mL, with a lower limit of detection of 5 pg/mL.

Outcomes

The primary outcome for this analysis was a composite of SPRINT's 6 pre-specified SAEs of interest: hypotension, syncope, electrolyte abnormalities, AKI, bradycardia, and injurious falls. Secondary outcomes included the 6 individual SAEs of interest composing the primary outcome. The first event for each SAE of interest, identified as an SAE or reported during an emergency department visit, was included. SAEs in SPRINT were defined as safety events meeting any of the following criteria: fatal or life-threatening, resulting in significant or persistent disability, requiring or prolonging hospitalization, or judged by the investigator to represent significant hazard or harm to the participant that might require medical or surgical intervention. SAEs were ascertained at study visits every 3 months using structured interviews, and between visits if study staff received notification of SAEs by trial participants, trial investigators involved in participant care, or electronic medical records. SPRINT safety officers at the Coordinating Center reviewed medical records from hospitalizations, emergency department visits, and SAE reports, and used the Medical Dictionary for Regulatory Activities version 14.0 to classify the SAEs. Up to 3 Medical Dictionary for Regulatory Activities codes were assigned to each event.

Hypotension was coded when symptomatic low BP, without specific BP cut-offs, was mentioned in the admission history and physical or discharge summary as a reason for admission. Syncope was coded with report of a sudden temporary loss of consciousness. Injurious fall was coded with report of a sudden, unintentional change in position in which the participant came to rest on the ground, floor, or a lower level not as the result of syncope or overwhelming external force. A fall because of syncope was not counted as an injurious fall, because syncope was captured separately. Bradycardia was coded with report of a symptomatic heart rate <40 beats per minute. Electrolyte abnormality was coded with serum sodium <132 or >150 mEq/L, or with serum potassium <3.0 or >5.5 mEq/L. AKI was coded if the diagnosis was noted in an emergency department visit without subsequent hospitalization, or if the diagnosis was listed in the hospital discharge summary and was believed by the safety officer to be 1 of the top 3 reasons for admission or continued hospitalization.

Covariates

Age, sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, or Hispanic/Other), medical history, medications, education level, alcohol use, and smoking status (current, former, or never) were obtained by questionnaire. Trained study coordinators measured BP using a standardized protocol, and recorded BP as the mean of 3 seated BP measurements taken 1 minute apart after a 5-minute rest period using an automated oscillometric device (Model 907; Omron Healthcare).[28] Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Fasting serum total cholesterol, high-density lipoprotein cholesterol, and triglycerides, serum creatinine and cystatin C, and urine albumin and creatinine were measured at the SPRINT Central Laboratory. Estimated GFR was calculated according to the Chronic Kidney Disease-Epidemiology Collaboration combined creatinine and cystatin C estimating equation.[29] Frailty status was defined according to a 36-item frailty index that classified people as fit (frailty index ≤0.10), less fit (0.10 < frailty index ≤0.21), or frail (frailty index >0.21).[30] A high total medication burden (prescribed antihypertensive and non-antihypertensive medications) was defined as a participant having ≥5 different prescription medications recorded at the baseline visit.[31]

Statistical Analysis

We tested for differences in baseline characteristics among those who did and did not develop an SAE using the Chi-squared test for categorical variables and the Wilcoxon rank sum test for continuous variables. Both hs-cTnT and NT-proBNP were $\log_2$-transformed to correct their right-skewed distributions. Consistent with our previous work, individual biomarkers were modeled as continuous, log-linear predictors and according to sex-specific tertiles. When we evaluated the biomarkers together, we categorized participants as having: (1) both biomarkers in the lower two tertiles, (2) one of the biomarkers in the highest tertile, or (3) both biomarkers in the highest tertile.

We used restricted cubic splines to assess whether each biomarker had an approximately linear association with the SAEs; we also used splines to estimate hazard ratios (HRs) at specific biomarker levels, relative to the median biomarker level. Because 21% of hs-cTnT levels

were below the limit of detection, we imputed undetectable values using a Tobit regression model applied to $\log_2$-transformed hs-cTnT to normalize its right-skewed distribution.[32] Three percent of NT-proBNP levels were below the limit of detection; we assigned these measurements a value of 3.5 pg/mL, equivalent to the lower limit of detection divided by the square root of 2.

In the primary analysis, we evaluated biomarker associations with risk of the composite SAE outcome using Cox proportional hazards models. SPRINT participants were censored at the first SAE, death, or the last available follow-up when the trial stopped in August 2015. In the secondary analysis of the 6 individual SAEs of interest, we considered that it was possible participants could experience multiple different SAEs (eg, AKI and hypotension), and that analyzing individual SAEs using separate Cox proportional hazards models would not account for the possible relationship between events. Therefore, we used the marginal approach of Wei-Lin-Weissfeld to Cox proportional hazards model to evaluate hs-cTnT and NT-proBNP associations with all 6 of the individual SAEs, concurrently. The Wei-Lin-Weissfeld model is a marginal model that assumes participants are simultaneously at risk for all SAEs and remain at risk for each SAE until it occurs.[33] Models constructed for each outcome were adjusted for the following potential baseline confounders: demographics (age, sex, race/ethnicity), intervention arm, clinical characteristics (BMI, alcohol use, smoking status, prevalent CVD, eGFR, and urine albumin-to-creatinine ratio), vitals (heart rate, systolic BP, diastolic BP, and orthostatic hypotension), dizziness, frailty index, medications (number of antihypertensive medications, antihypertensive medication class, statin use, and total medication burden), and the other cardiac biomarker. There was no evidence that the proportional hazards assumptions were violated. Potential modification of the randomized treatment assignment effect on SAE risk across combined biomarker categories was assessed using a likelihood ratio test. We also evaluated whether hs-cTnT and NT-proBNP associations with the composite SAE outcome varied by baseline eGFR <60 versus ≥60 mL/min per 1.73 m^2, baseline systolic BP <140 versus ≥140 mm Hg, baseline diastolic BP <70 versus ≥70 mm Hg, prevalent CVD, frailty index, age, and sex in multivariable adjusted models using a likelihood ratio test.

All analyses were conducted using the SAS system, version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Of the 9361 SPRINT participants, 8828 (94.3%) had hs-cTnT (median [interquartile range] 9.4 [6.4–14.1] ng/L] and 8836 (94.4%) had NT-proBNP (median [interquartile range] 86 [37–197] pg/mL) measured at baseline. Baseline hs-cTnT and NT-proBNP were moderately correlated (correlation coefficient=0.39). After a median 3.0 years of follow-up, 1412 (16.0%) experienced ≥1 of the SAEs of interest. Compared with participants who did not have an SAE, participants who experienced ≥1 SAE had higher median baseline levels of hs-cTnT (11.5 ng/L versus 9.0 ng/L, $P<0.001$) and NT-proBNP (151 pg/mL versus 78 pg/mL, $P<0.001$), and were older, more often White and women, more likely to be randomized to the intensive arm of the trial, and had slightly higher systolic BP and lower diastolic BP at baseline. They also had a higher burden of comorbidities (Table 1).

The proportion of participants who experienced the composite SAE outcome and each of the individual SAEs was higher across sex-specific tertiles of hs-cTnT and NT-proBNP, particularly for combined biomarker categories (Table 2 and Figure 1). Eleven percent of participants with both hs-cTnT and NT-proBNP in the lower two tertiles experienced the composite SAE whereas 30% of participants with both hs-cTnT and NT-proBNP in the highest tertile experienced the composite SAE.

Restricted cubic spline plots show a graded association between higher hs-cTnT and NT-proBNP concentrations and risk of the composite SAE (Figure 2). While the association between hs-cTnT and the composite SAE appeared linear (test for non-linearity $P=0.19$), the association between NT-proBNP and the composite SAE was flat at concentrations below the median, and then increased thereafter (test for non-linearity $P<0.001$). In multivariable models adjusting for demographics, clinical characteristics, intervention arm, and the other cardiac biomarker, elevations in hs-cTnT and NT-proBNP were each independently associated with higher risk of the composite SAE (Table 3). When we considered combined biomarker categories, participants with both hs-cTnT and NT-proBNP in the highest tertile had significantly higher risk of the composite SAE compared with participants with biomarkers in the lower two tertiles in multivariable analyses.

Individual biomarker associations with the composite SAE appeared somewhat stronger in the standard arm compared with the intensive arm, although tests for biomarker-by-treatment interactions were not significant (P for interaction=0.23 for hs-cTnT, P for interaction=0.056 for NT-proBNP, Table 3). In contrast, compared with participants with both biomarkers in the lower tertiles, those who had both hs-cTnT and NT-proBNP in the highest tertile appeared to have a stronger association with the composite SAE outcome in the standard arm (HR, 1.88; 95% CI, 1.52–2.32) than in the intensive arm (HR, 1.33; 95% CI, 1.08–1.62; P for interaction=0.008).

Table 1. Baseline Characteristics of SPRINT Participants Stratified by Development of SAEs of Interest During Follow-Up

Characteristic	No SAE of interest*(n=7424)	≥1 SAE of interest (n=1412)	*P* value
Intensive BP arm	3641 (49%)	782 (55%)	<0.001
Age, y	66 (60–75)	73 (64–79)	<0.001
Women	2672 (36%)	579 (41%)	<0.001
Race			
White	5051 (68%)	1028 (73%)	<0.001
Black	2223 (30%)	366 (26%)	
Other†	150 (2%)	18 (1%)	
Hispanic	874 (12%)	71 (5%)	<0.001
Smoking			
Current	971 (13%)	178 (13%)	0.017
Former	3017 (41%)	631 (45%)	
Never	3435 (46%)	603 (43%)	
Alcohol use (y/n)	4781 (64%)	881 (62%)	0.15
Frailty index >0.21	2269 (31%)	639 (45%)	<0.001
Prevalent CVD	1392 (19%)	362 (26%)	<0.001
Prevalent heart failure	215 (3%)	86 (6%)	<0.001
eGFR, mL/min per 1.73 m^2	76 (60–90)	65 (47–81)	<0.001
eGFR <60 mL/min per1.73 m^2	1824 (25%)	603 (43%)	<0.001
Urine ACR, mg/g	9.2 (5.6–19.3)	13.1 (6.5–37.3)	<0.001
Heart rate, bpm	65 (58–74)	65 (58–73)	0.19
Systolic BP, mm Hg	138 (130–149)	140 (130–150)	0.046
Diastolic BP, mm Hg	79 (71–86)	75 (68–84)	<0.001
Total medication burden ≥5	3148 (42%)	826 (58%)	<0.001
No. antihypertensive medications	2.0 (1.0–2.0)	2.0 (1.0–3.0)	<0.001
Antihypertensive med class			
Beta blocker	2604 (35%)	634 (45%)	<0.001
Diuretic	3416 (46%)	682 (48%)	0.11
Calcium channel blocker	2571 (35%)	545 (39%)	<0.01
ARB	1624 (22%)	315 (22%)	0.72
ACEi	2515 (34%)	527 (37%)	0.013
BMI, kg/m^2	29 (26–33)	28 (25–32)	<0.001
HDL cholesterol, mg/dL	50 (43–60)	52 (44–64)	<0.001
Statin use	3115 (42%)	703 (50%)	<0.001
hs-cTnT, ng/L	9.0 (6.3–13.5)	11.5 (7.5–18.0)	<0.001
NT-proBNP, pg/mL	78 (35–173)	151 (63–376)	<0.001

Data displayed are n (%) or median (interquartile range). ACEi indicates angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAEs, serious adverse events; and SPRINT, Systolic Blood Pressure Intervention Trial.

*Serious adverse events include hypotension, syncope, bradycardia, electrolyte abnormalities, injurious fall, or acute kidney injury that were either documented in an emergency department visit or were reported in a serious adverse event, defined as a fatal or life threatening event, resulting in significant or persistent disability, requiring or prolonging hospitalization, or judged important medical event.

†Other includes participants who did not self-identify as belonging to White or Black race categories.

This interaction was further demonstrated when evaluating the effect of randomization on composite SAE risk stratified by combined biomarker categories (Figure 3). Randomization to the intensive arm versus standard arm was associated with higher risk of the composite SAE outcome among participants with both biomarkers in the lower two tertiles (13% versus 9%, *P*<0.001) and among participants with one biomarker in the highest tertile (19% versus 13%, *P*<0.001). Conversely, there was no association between randomization arm and risk of the composite SAE outcome among participants with both biomarkers in the highest tertile (30% versus 29%, *P*=0.85).

Table 2. Number of SPRINT Participants With SAEs of Interest, Stratified by Sex-Specific Tertiles of hs-cTnT and NT-proBNP, Individually and in Combination

Adverse events	Biomarker tertiles		
	hs-cTnT Tertile 1 (n=3022) (n, %) Men: <6–8.4 ng/L Women: <6 ng/L	**hs-cTnT Tertile 2 (n=2863) (n, %) Men: 8.5–13.5 ng/L Women: 6.0–9.5 ng/L**	**hs-cTnT Tertile 3 (n=2943) (n, %) Men: >13.5 ng/L Women: >9.5 ng/L**
Composite SAE	323 (11%)	413 (14%)	675 (23%)
Individual SAEs			
AKI	49 (2%)	73 (3%)	185 (6%)
Hypotension	68 (2%)	82 (3%)	88 (3%)
Syncope	63 (2%)	104 (4%)	99 (3%)
Bradycardia	26 (0.9%)	46 (2%)	111 (4%)
Electrolyte abnormality	69 (2%)	92 (3%)	134 (5%)
Injurious fall	133 (4%)	173 (6%)	330 (11%)
	NT-proBNP Tertile 1 (n=2935) Men: <5–42 pg/mL Women: <5–68 pg/mL	**NT-proBNP Tertile 2 (n=2960) Men: 43–125 pg/mL Women: 69–174 pg/mL**	**NT-proBNP Tertile 3 (n=2941) Men: >125 pg/mL Women: >174 pg/mL**
Composite SAE	301 (10%)	385 (13%)	726 (25%)
Individual SAEs			
AKI	54 (2%)	62 (2%)	192 (7%)
Hypotension	67 (2%)	57 (2%)	114 (4%)
Syncope	68 (2%)	86 (3%)	112 (4%)
Bradycardia	20 (0.7%)	43 (1%)	120 (4%)
Electrolyte abnormality	66 (2%)	69 (2%)	160 (5%)
Injurious fall	117 (4%)	178 (6%)	341 (12%)
	Tertiles 1 or 2 of both hs-cTnT and NT-proBNP (n=4624)	**Tertile 3 of one of hs-cTnT or NT-proBNP (n=2527)**	**Tertile 3 of both hs-cTnT and NT-proBNP (n=1677)**
Composite SAE	508 (11%)	406 (16%)	497 (30%)
Individual SAEs			
AKI	77 (2%)	84 (3%)	146 (9%)
Hypotension	97 (2%)	80 (3%)	61 (4%)
Syncope	122 (3%)	77 (3%)	67 (4%)
Bradycardia	38 (0.8%)	59 (2%)	86 (5%)
Electrolyte abnormality	108 (2%)	80 (3%)	107 (6%)
Injurious fall	209 (5%)	183 (7%)	244 (15%)

AKI indicates acute kidney injury; hs-cTnT, high-sensitivity cardiac cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAEs, serious adverse events; and SPRINT, Systolic Blood Pressure Intervention Trial.

Hs-cTnT and NT-proBNP associations with risk of the composite SAE did not vary by subgroups of baseline systolic BP, diastolic BP, CVD, frailty, age, and sex (*P* for interaction >0.20 for all, Figure S1). Hs-cTnT associations appeared somewhat stronger in participants with baseline eGFR <60 mL/min per 1.73 m^2 (HR 1.23, 95% CI, 1.10–1.37) compared with those with eGFR ≥60 mL/min per 1.73 m^2 (HR, 1.09; 95% CI, 0.98–1.22), although the test for interaction was not significant (*P*=0.11).

We next modeled hs-cTnT and NT-proBNP associations with risk of the individual SAEs of interest (Table S1). In multivariable adjusted models, higher hs-cTnT was independently associated with a higher risk of AKI, bradycardia, and injurious falls, while higher NT-proBNP was independently associated with a higher risk of bradycardia, electrolyte abnormalities, and injurious falls. Neither biomarker was individually associated with syncope or hypotension, although having both biomarkers in the highest tertile compared with the lower tertiles was associated with a lower risk of syncope. When compared across combined biomarker categories, each SAE occurred more frequently in the intensive arm compared with the standard arm, although injurious falls occurred more frequently in the standard arm among

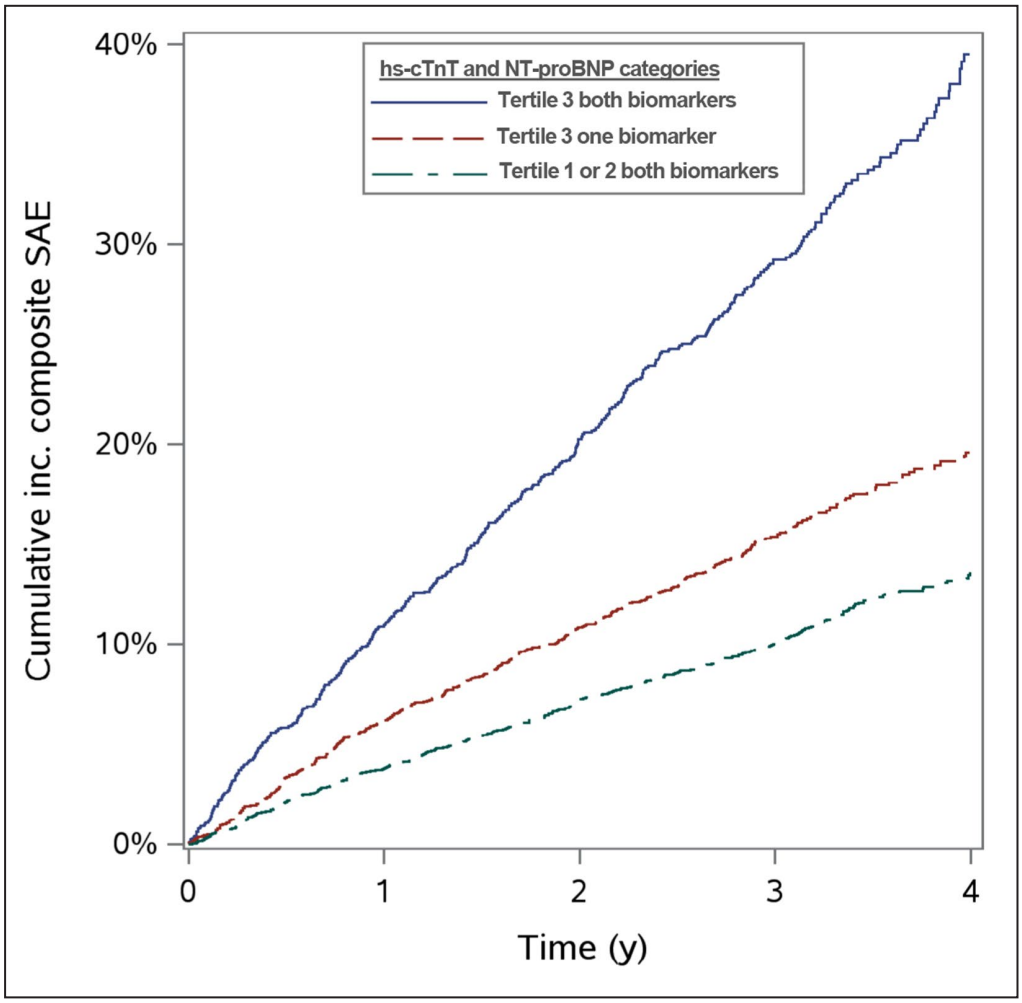

Figure 1. Cumulative incidence of the composite SAE outcome stratified by combined hs-cTnT and NT-proBNP categories.
Composite SAE outcome indicates hypotension, syncope, bradycardia, acute kidney injury, electrolyte abnormalities, or injurious falls. Combined biomarker categories include: (1) both hs-cTnT and NT-proBNP in the lower two sex-specific tertiles, (2) one of hs-cTnT or NT-proBNP in the highest sex-specific tertile, (3) both hs-cTnT and NT-proBNP in the highest sex-specific tertile. hs-cTnT indicates high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and SAE, serious adverse event.

those in the highest combined biomarker category. (Figure S2).

DISCUSSION

In this cardiac biomarker analysis of SPRINT, elevations in hs-cTnT and NT-proBNP were independently associated with higher risk of the composite SAE outcome, and the highest SAE risk was observed among individuals with both biomarkers in the highest tertile. While the higher composite SAE risk in the intensive-treatment group versus the standard-treatment group has been previously noted, we showed that composite SAE risk was similar irrespective of intervention arm among those with both hs-cTnT and NT-proBNP in the highest tertile.[3] These findings suggest that these two widely available blood tests with strong associations with CVD risk also provide prognostic information about SAE risk during hypertension treatment. If our findings are confirmed, the differential risk of SAEs across treatment arms may have utility for identifying individuals who may receive the greatest benefit without increased risk of harm with intensive BP lowering compared with standard BP lowering.

We found that the intensive-treatment group and the standard-treatment group had similar composite SAE risk among SPRINT participants with both biomarkers in the highest tertile; this contrasts with our recent study demonstrating that intensive BP lowering

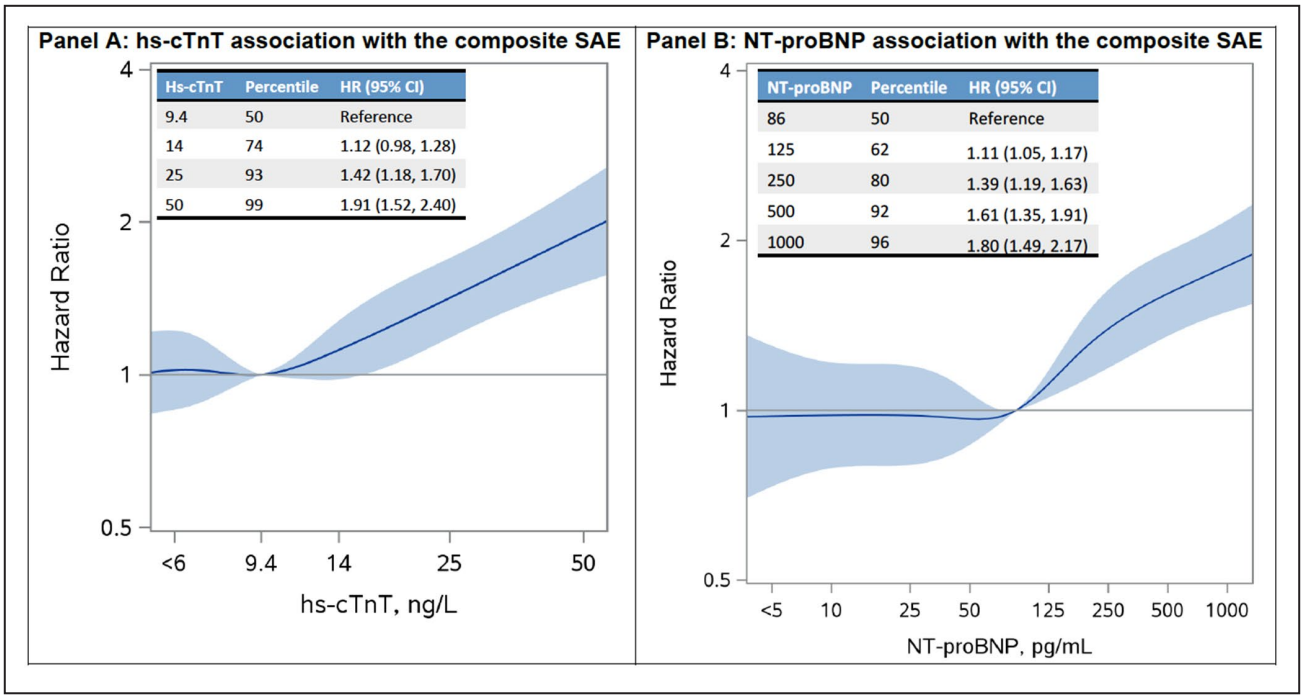

Figure 2. Restricted cubic splines of hazard ratios and 95% CIs for the associations of hs-cTnT and NT-proBNP with risk of the composite SAE outcome.
The composite SAE outcome indicates hypotension, syncope, bradycardia, acute kidney injury, electrolyte abnormalities, or injurious falls. Hazard ratios (solid blue lines) with 95% confidence intervals (shaded areas) for the composite SAE outcome by baseline hs-cTnT (panel **A**) and NT-proBNP (panel **B**) levels are displayed. Estimates were obtained from multivariable Cox proportional hazards models that included demographics (age, sex, race), intervention arm, cardiovascular risk factors (body mass index, alcohol use, smoking status, prevalent cardiovascular disease, estimated glomerular filtration rate, and urine albumin-to-creatinine ratio), vitals (heart rate, systolic BP, diastolic BP, and orthostatic hypotension), dizziness, frailty, medications (statin use, total medication burden, number of antihypertensive medications, and antihypertensive medication class), and the other cardiac biomarker. BP indicates blood pressure; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and SAE, serious adverse event.

had the greatest absolute risk reductions in all-cause mortality among individuals with elevated hs-cTnT and NT-proBNP. For example, the 4-year absolute risk reduction of randomization to the intensive-treatment group versus standard-treatment group for all-cause mortality among individuals without elevated hs-cTnT and NT-proBNP was 0.97%, whereas the 4-year absolute risk reduction was 7.00% among individuals with both biomarkers elevated.[23] We speculate that participants with high cardiac biomarker levels have substantial multimorbidity at baseline that predisposes them to SAEs regardless of their lower achieved BP and use of additional antihypertensive medications following randomization to the intensive-treatment group. These findings suggest that combined elevations in hs-cTnT and NT-proBNP indicate a high SAE risk, but also identify a subset with substantial absolute benefit from intensive BP lowering and no excess risk of harms compared with standard BP lowering. However, this interesting finding was not a pre-specified hypothesis and requires confirmation before hypertension treatment decisions are altered in clinical practice. Prospective biomarker testing as part of a randomized clinical trial is needed to evaluate whether incorporating cardiac biomarkers into hypertension treatment decisions could help personalize the benefit-harm trade-offs of intensive BP lowering.

The development of hypertension treatment strategies that facilitate safe BP lowering is important given the worsening trends in BP control among US adults.[34] In addition, the rising numbers of individuals requiring pharmacotherapy to achieve BP control and lower BP targets will increase the burden of SAEs. A simulation study demonstrated that full implementation of the 2017 American College of Cardiology/American Heart Association blood pressure guideline among all eligible US adults would prevent an estimated 3 million CVD events over a 10-year period, but also lead to 3.3 million SAEs.[35] It should be noted, however, that most SAEs in SPRINT were transient and treatable, and are likely less consequential than CVD events.

To our knowledge, the associations of hs-cTnT and NT-proBNP with SAEs in a hypertension trial were previously unknown, and the mechanisms through

Table 3. Associations of hs-cTnT and NT-proBNP With Risk of the Composite SAE Outcome in SPRINT Participants, Overall and Stratified by Intervention Arm

Biomarker	HR (95% CI)*			
	Overall (n=8836)	Intensive BP arm (n=4423)	Standard BP arm (n=4413)	*P* for interaction
Hs-cTnT				
Per 2-fold higher	1.15 (1.06–1.25)	1.11 (1.00–1.23)	1.20 (1.08–1.34)	0.23
Tertile 1	Reference	Reference	Reference	0.59
Tertile 2	0.99 (0.84–1.15)	0.94 (0.77–1.15)	1.05 (0.83–1.34)	
Tertile 3	1.11 (0.94–1.31)	1.03 (0.84–1.28)	1.21 (0.95–1.54)	
NT-proBNP				
Per 2-fold higher	1.09 (1.05–1.14)	1.06 (1.01–1.12)	1.13 (1.07–1.19)	0.056
Tertile 1	Reference	Reference	Reference	0.13
Tertile 2	0.97 (0.83–1.14)	0.93 (0.75–1.14)	1.04 (0.81–1.32)	
Tertile 3	1.37 (1.15–1.62)	1.19 (0.96–1.47)	1.63 (1.28–2.09)	
Combined biomarkers				
Tertile 1 or 2 both biomarkers	Reference	Reference	Reference	0.0082
Tertile 3 one biomarker	1.08 (0.94–1.25)	1.09 (0.91–1.30)	1.07 (0.86–1.32)	
Tertile 3 both biomarkers	1.56 (1.32–1.84)	1.33 (1.08–1.62)	1.88 (1.52–2.32)	

BP indicates blood pressure; HR, hazard ratio; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAE, serious adverse event; and SPRINT, Systolic Blood Pressure Intervention Trial.

*Models were adjusted for age, demographics (sex, race, education), intervention arm, prevalent cardiovascular disease, smoking, alcohol use, frailty index, body mass index, estimated glomerular filtration rate, urine albumin-to-creatinine ratio, heart rate, systolic blood pressure, diastolic blood pressure, orthostatic hypotension, dizziness, number of antihypertensive medications at baseline, antihypertensive medication class, total medication burden, the other cardiac biomarker and treatment x biomarker interaction.

which cardiac biomarkers signal SAE risk during hypertension treatment remain unclear. Cohort studies in older adults have shown that higher concentrations of hs-cTnT and NT-proBNP are associated with risk of falls, orthostatic hypotension, and hospitalizations with AKI.[24–26] Elevated hs-cTnT and NT-proBNP may reflect a diminished cardiac capacity to tolerate hemodynamic changes that can occur during episodes of acute illness while on antihypertensive therapy. Alternatively, cardiac biomarkers may reflect other pathologic processes that contribute to both subclinical cardiac disease and SAE risk. For example, low diastolic BP may lead to myocardial injury from lower coronary perfusion pressures and thus link hs-cTnT with higher risk of SAEs.[36–38] Renin-angiotensin-aldosterone system over-activity can lead to ventricular pressure and volume overload – the primary drivers of NT-proBNP secretion – and contribute to the severity of AKI via intra-renal renin-angiotensin-aldosterone system activation.[39,40] Further investigations into the cardiac-mediated mechanisms of SAEs are warranted.

Our study has several limitations. First, because of the SPRINT design, our findings may not be generalizable to adults at younger ages, individuals with diabetes, those with low or intermediate CVD risk, or those with advanced heart failure. Second, participants were not masked to treatment assignment, and those in the intensive arm had 30% more study visits; this may have led to ascertainment bias because of over-reporting of SAEs among participants receiving intensive BP lowering. However, this was unlikely to affect biomarker associations with SAEs. Third, SAEs were prospectively identified and not masked to investigators, which may have led to detection bias. Fourth, some SPRINT participants may have had undiagnosed heart failure that led to higher baseline cardiac biomarker levels, although this would be unlikely to affect the biomarker associations with SAE risk. Finally, because of the potential for type I error because of multiple comparisons, analyses of individual SAEs of interest should be interpreted as exploratory.

In summary, this study demonstrated that baseline hs-cTnT and NT-proBNP levels were associated with risk of SAEs in SPRINT. In addition, the impact of randomization to the intensive arm on composite SAE risk varied by combined biomarker groups. Our findings provide insight into the role of subclinical myocardial injury and neurohormonal stress in the development of SAEs during hypertension treatment. Furthermore, if our findings are confirmed, they support the development of a future trial testing the role of these widely available blood biomarkers in characterizing the benefits and harms of hypertension treatment decisions.

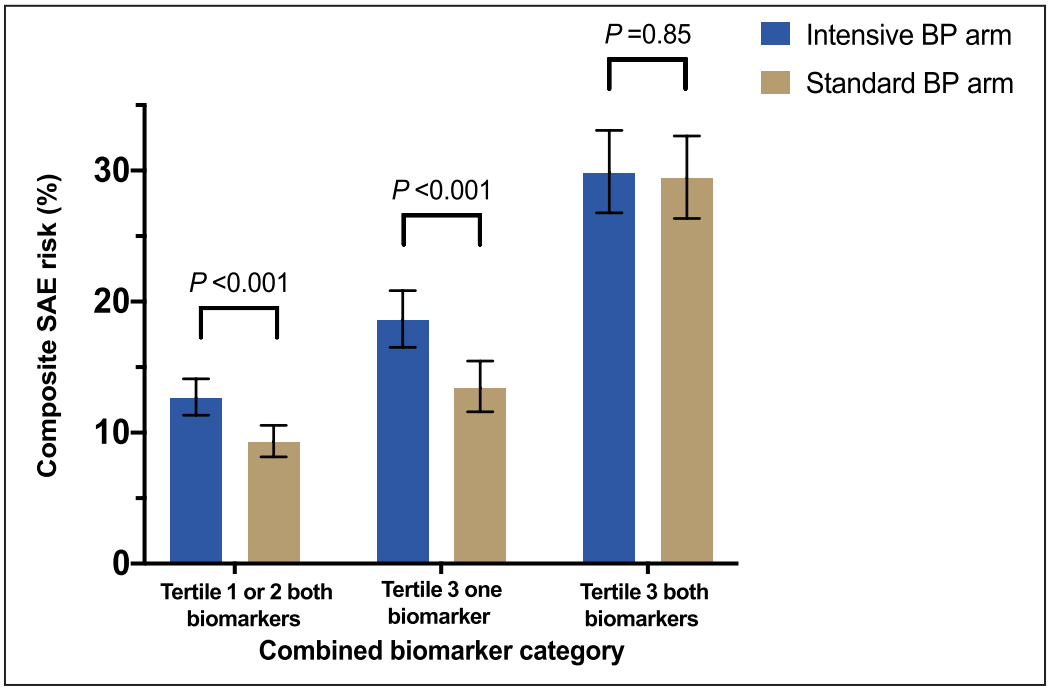

Figure 3. Proportion of SPRINT participants who experienced the composite SAE outcome stratified by combined hs-cTnT and NT-proBNP categories
Composite SAE outcome indicates hypotension, syncope, bradycardia, acute kidney injury, electrolyte abnormalities, or injurious falls. Combined biomarker categories include: (1) both hs-cTnT and NT-proBNP in the lower two sex-specific tertiles, (2) one of hs-cTnT or NT-proBNP in the highest sex-specific tertile, (3) both hs-cTnT and NT-proBNP in the highest sex-specific tertile. BP, blood pressure; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide and SAE, serious adverse event.

ARTICLE INFORMATION

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Supplemental Material

Table S1
Figures S1–S2

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