Effect of Lowering Diastolic Pressure in Patients With and Without Cardiovascular Disease: Analysis of the SPRINT (Systolic Blood Pressure Intervention Trial)

Nadia A. Khan, Simon W. Rabkin, Yinshan Zhao, Finlay A. McAlister, Julie E. Park, Meijiao Guan, Sammy Chan, Karin H. Humphries

Abstract — Systolic and diastolic blood pressure thresholds, below which cardiovascular events increase, are widely debated. Using data from the SPRINT (Systolic Blood Pressure Intervention Trial), we evaluated the relation between systolic and diastolic pressure and cardiovascular events among 1519 participants with or 7574 without prior cardiovascular disease. Using Cox regression, we examined the composite risk of myocardial infarction, other acute coronary syndrome, stroke, heart failure, or cardiovascular death, and follow-up systolic and diastolic pressure were analyzed as time-dependent covariates for a median of 3.1 years. Models were adjusted for age, sex, baseline systolic pressure, body mass index, 10-year Framingham risk score, and estimated glomerular filtration rate. A J-shaped relationship with diastolic pressure was observed in both treatment arms in patients with or without cardiovascular disease (P nonlinearity ≤ 0.002). When diastolic pressure fell < 55 mm Hg, the hazards were at least 25% higher relative to 70 mm Hg (P ≤ 0.29). The hazard ratios (95% CI) of diastolic pressure < 55 mm Hg versus 55 to 90 mm Hg were 1.68 (1.16–2.43), P value 0.006 and 1.52 (0.99–2.34), P value 0.06 in patients without and with prior cardiovascular disease, respectively. After adjusting for follow-up diastolic pressure, follow-up systolic pressure was not associated with the outcome in those without prior cardiovascular disease (P = 0.64). In those with cardiovascular disease, adjusting for diastolic pressure, follow-up systolic pressure was associated with the risk in the intensive arm (hazard ratio per 10 mm Hg decrease, 0.86; 95% CI, 0.75–0.99; P interaction = 0.02). Although the observed J-shaped relationship may be because of reverse causality in the SPRINT population, we advise caution in aggressively lowering diastolic pressure. (Hypertension. 2018;71:840-847. DOI: 10.1161/HYPERTENSIONAHA.117.10177.) • Online Data Supplement

Key Words: blood pressure • cardiovascular disease • heart failure • hypertension • myocardial infarction

The landmark SPRINT (Systolic Blood Pressure Intervention Trial) determined that intensively lowering systolic blood pressure (SBP) to <120 mm Hg was associated with reduced mortality and cardiovascular events compared with standard SBP control of <140 mm Hg. However, patients, healthcare providers, and guideline bodies have been reluctant to reduce BP to these lower targets given concern over increased risk of adverse events if BP falls too low. This J-curve phenomenon, where the risk of adverse events increases when a lower BP threshold is breached, has been widely debated. Although physiologically it is known that at some lower BP threshold, organ perfusion becomes impaired and cardiovascular risk should increase, the exact BP threshold remains unclear. Further, whether this threshold differs in patients with obstructive coronary disease who may be vulnerable to reduced coronary perfusion during diastole is a point of debate. Most of the earlier studies did not prospectively target low enough BPs to determine a true nadir. As such, these studies were unable to exclude reverse causation at lower extremes of BP, an epiphenomenon where achieved low diastolic pressure may reflect other conditions associated with cardiovascular risk including frailty, malignancy, malnourishment, or reduced systolic function.

The SPRINT trial therefore provides a unique opportunity to assess lower extremes of systolic and diastolic pressure in an at-risk population of patients without diabetes mellitus, history of stroke, or heart failure. Using these data, we examined the relationship between lower SBP and diastolic BP (DBP) and risk for combined cardiovascular disease (CVD) events in those with and without CVD. We also examined clinical predictors of developing low DBP.

Methods

The SPRINT data were made available as part of a New England Journal of Medicine/National Heart, Lung, and Blood Institute initiative.
Anonymized data were made publicly available at the New England Journal of Medicine/National Heart, Lung, and Blood Institute and can be accessed at https://biolinc.nhlbi.nih.gov/studies/sprint_pop.

Study Population
The details of the SPRINT trial are published elsewhere. In brief, this randomized, open-label, controlled trial included 9361 patients aged 50 years and older with a screening SBP of 130 to 180 mm Hg. Patients were included if they were 50 to 75 years with at least one of the following: an increased risk for CVD defined as a history of clinical or subclinical CVD, chronic kidney disease (estimated glomerular filtration rate 20–60 mL/min 1.73 m2), 10-year Framingham CVD risk of 15% or higher; or if patients were aged 75 years or older. Patients were excluded from SPRINT if they had diabetes mellitus, heart failure, or previous stroke.

For this post hoc analysis, patients who experienced a cardiovascular event within 30 days of randomization, did not have any recorded BPs after randomization, or had missing key baseline characteristics were excluded. Therefore, follow-up was from 30 days post-randomization to the primary outcome, or noncardiovascular death, whichever came first. Patients were also stratified by history of clinical CVD using the SPRINT definition of clinical CVD (a prespecified subgroup in SPRINT). Clinical CVD (other than stroke) was defined as any of (1) previous myocardial infarction (MI), percutaneous coronary intervention, coronary artery bypass grafting, carotid endarterectomy, carotid stenting, (2) peripheral artery disease with revascularization, (3) acute coronary syndrome with or without resting ECG change, ECG changes on a graded exercise test, or positive cardiac imaging study, (4) at least a 50% diameter stenosis of a coronary, carotid, or lower extremity artery, or (5) abdominal aortic aneurysm ≥5 cm with or without repair.

Procedures
SPRINT patients were randomized in 1:1 fashion to intensive BP lowering to a systolic target of <120 mm Hg versus standard SBP lowering of 135 to 139 mm Hg. There were no diastolic targets. Care providers followed a treatment algorithm emphasizing long-acting thiazide-type diuretics, but the algorithm did not restrict antihypertensive medication choices. The study was originally planned for a 5-year follow-up, but ended early because of clear evidence of treatment benefit (median follow-up, 3.26 years).

BP Measurements
A mean of 3 seated BPs was used to determine baseline and follow-up visit BPs using a fully automated validated BP device after a period of 5 minutes of quiet rest with the patient alone in the room. BP measurements were scheduled at baseline, months 1, 2, 3 and every 3 months until the study end.

Composite Cardiovascular Outcome
The primary outcome selected for this analysis was identical to the primary outcome in the SPRINT trial, namely a composite end point of MI, non-MI acute coronary syndrome, stroke, acute decompensated heart failure, or death from cardiovascular causes. The definitions of MI and non-MI acute coronary syndrome used standard definitions including combination of symptom presentation, cardiac biomarker elevation, and ECG changes. Non-MI acute coronary syndrome required evidence of coronary ischemia but without meeting the definition of MI. Stroke is defined using standard definitions including symptoms and signs, as well as brain and cerebrovascular imaging. Heart failure was defined as diagnosed acute or subacute decompensated heart failure indicated by multiple signs of heart failure and requiring hospitalization or emergency department visit with intravenous treatment for heart failure. All outcomes were adjudicated, and the details are presented elsewhere. We also examined (1) the composite of primary outcome and all-cause mortality as low BP is associated with noncardiac conditions and total mortality, and (2) individual components of the primary outcome (online-only Data Supplement).

Statistical Analysis
To evaluate the relation between follow-up BP and risk of cardiovascular events, multivariable Cox regressions were performed separately for patients with or without a history of clinical CVD. For the primary outcome, if a patient died because of a noncardiovascular death without reaching the study outcome, the follow-up time was censored at the time of death. If the follow-up BP visits ended before the final event ascertainment, patients were censored at 6 months after the final BP visit. The achieved follow-up SBP and DBP at each visit were analyzed as time-dependent covariates. Because a nonlinear relationship between the BP measures and the log hazard was expected, the natural cubic spline was applied. Nonlinearity was evaluated using the likelihood ratio test. If nonlinearity was confirmed, the number of knots was then determined using the Akaike information criterion. Two main models were constructed: the first, only examining follow-up systolic pressure and the second with both follow-up systolic and diastolic pressure. Our initial analysis indicated that the correlation between follow-up DBP and SBP was only moderate (r=0.54; Figure 1); therefore, it was feasible to include both SBP and DBP in the same model. Both models were adjusted for randomization group, baseline systolic pressure, and other prognostic factors selected using a backward stepwise procedure. Age, sex, body mass index, Framingham 10-year cardiovascular risk score, and estimated glomerular filtration rate were adjusted in the final analyses. We also categorized the follow-up diastolic and systolic pressures in 3 discrete categories (<55, 55–90, and >90 mm Hg for DBP and ≤120, 121–150, and >150 mm Hg for SBP). Two-way interactions between the BP measures and treatment strategy were assessed. Analysis by treatment arm and interactions by sex and age are shown in the online-only Data Supplement. A P value <0.1 for interaction terms was considered significant.

We evaluated risk predictors for a follow-up DBP measure falling <55 mm Hg, chosen based on risk level evaluated in the Cox regression analysis, using a logistic regression model with patient-specific random intercepts. Factors examined included sex, race (non-Hispanic black, Hispanic, non-Hispanic white, and other), study duration, and baseline factors (age, body mass index, smoking status [never, former, current]), baseline SBP and DBP, prior CVD, triglycerides (on the log scale), cholesterol, and creatinine (on the log scale). Interactions between treatment and other factors were examined.

All analyses were performed using RStudio (1.0.136), with the package rms and SAS 9.4 (Cary, NC). The SPRINT data were made available as part of a New England Journal of Medicine/National Heart, Lung, and Blood Institute initiative. This study was approved by the University of British Columbia ethics board.

Results
There were 7574 patients without CVD and 1519 patients with CVD in our analysis after exclusions; 225 (2.9%); 109 experienced an event or lost to follow-up <30 days; 36 without at least 1 follow-up BP; 80 with missing baseline data) and 43 (2.8%); 26 experienced an event or lost to follow-up <30 days; 8 without at least 1 follow-up BP; 9 with missing baseline data) patients without and with clinical CVD, respectively, were excluded. There was no significant difference in proportion of those excluded by treatment assignment in those with and without CVD (P=0.81). Median follow-up time after exclusions was 3.1 years regardless of treatment arm and history of CVD, with an average of 13 follow-up BP visits.

Patients without CVD were younger, more likely to be female, or non-Hispanic black compared with those with CVD (Table 1). Those without CVD had a higher baseline BP and were taking fewer antihypertensive agents, but had a lower average 10-year Framingham risk score compared with those with CVD.
Follow-up SBP and DBP are shown in Figure 1 and Table 2. BPs were lower in those assigned intensive treatment versus standard treatment targets. Achieved SBP was also similar in those with and without CVD, but achieved DBP was lower in those with CVD compared with those without CVD. The correlations between baseline and SBP measured in the first 3 months after baseline was 0.24 and 0.13 for the later visits.

Cohort Without CVD

There were 3773 persons without CVD randomized to standard treatment (193 reached the primary outcome) and 3801 randomized to intensive treatment (138 reached the primary outcome).

Follow-Up SBP and the Primary Outcome

In the model without diastolic pressure, the relationship between follow-up SBP and the primary outcome was nonlinear (P=0.03), although a distinct J-shaped relationship was only observed in the standard group (Figure S1 in the online-only Data Supplement). When analyzing the follow-up SBP as a categorical variable, in the intensive BP-lowering group, achieving an SBP of ≤120 mm Hg was associated with a significant reduction in cardiovascular events, compared with achieved SBPs of 121 to 150 mm Hg in the standard arm (hazard ratio [HR], 0.64; 95% CI, 0.48–0.86). In the standard treatment group, lowering SBP to ≤120 mm Hg was associated with a nonsignificant increase in cardiovascular events compared with achieved SBP of 121 to 150 mm Hg in the standard arm (HR, 1.38; 95% CI, 0.92–2.06).

Follow-Up DBP and the Primary Outcome

When additionally accounting for follow-up diastolic pressure, there was no evidence of a nonlinear relationship (J curve) between follow-up SBP and the primary composite outcome. Therefore, a linear association was assumed, and the association was not significant (HR per 10 mm Hg decrease in follow-up SBP, 0.98; 95% CI, 0.89–1.07; P=0.64).

As seen in Figure 2 (left), there was a J-shaped association between DBP and the composite cardiovascular outcome regardless of intensive or standard treatment strategy (P non-linearity<0.001; P interaction=0.47). When plotted by treatment arm (Figure S2, left), the patterns were similar in both arms. As noted in Figure 2, the hazards increased when DBP was <55 or >95 mm Hg (ie, ≈25% higher hazard compared with 70 mm Hg). When considering DBP as a categorical variable, the HRs of DBP <55 and >90 mm Hg relative to DBP between 55 and 90 mm Hg were 1.68 (95% CI, 1.16–2.43) and 1.45 (95% CI, 0.89–2.35), respectively.

Cohort With CVD

There were 754 persons with CVD randomized to standard treatment (93 reached the primary outcome) and 765 randomized to intensive treatment (83 reached the primary outcome).

Follow-Up SBP and the Primary Outcome

In the model without diastolic pressure, there was no evidence of a J curve between follow-up SBP and the primary composite outcome. Therefore, a linear association was assumed. The
The effect of follow-up SBP on the composite cardiovascular end point differed by treatment assignment ($P_{\text{interaction}}=0.05$). In the standard treatment group, the hazard did not change significantly with follow-up SBP (HR per 10 mm Hg decrease, 1.06; 95% CI 0.92–1.22; $P=0.44$). However, in the intensive treatment group, the hazard of developing a cardiovascular
event decreased with decreasing follow-up SBP (HR per 10 mm Hg decrease, 0.87; 95% CI, 0.77–1.00; \( P = 0.04 \)). As a result, the treatment benefit was more evident among those achieved a lower SBP (intensive versus standard arm HR, 0.74; 95% CI, 0.51–1.07 at 120 mm Hg; HR, 1.59; 95% CI, 0.84–3.02 at 160 mm Hg).

Supplementary Analysis
There was a significant interaction between age and follow-up DBP, but not sex (Figure S3). The analysis of the primary outcome and all-cause mortality also demonstrated a nonlinear J-shaped curve with follow-up DBP (data not shown) and for

Table 2. Summary of Achieved SBP and DBP by Treatment Arm and Prior CVD Status (All Follow-Up Visits Pooled)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients Without CVD</th>
<th>Patients With CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Standard</td>
</tr>
<tr>
<td>No. of patients</td>
<td>3801</td>
<td>3773</td>
</tr>
<tr>
<td>No. of visits</td>
<td>50,618</td>
<td>49,828</td>
</tr>
<tr>
<td>SBP (mm Hg); Median (25th, 75th percentile)</td>
<td>119 (113, 128)</td>
<td>135 (127, 142)</td>
</tr>
<tr>
<td>DBP (mm Hg); Median (25th, 75th percentile)</td>
<td>68 (62, 75)</td>
<td>76 (68, 83)</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

Follow-Up DBP and SBP and the Primary Outcome
After including follow-up DBP, the association between follow-up SBP and the primary composite outcome was similar to the model with follow-up SBP alone.

As seen in Figure 2 (right), there was a J-shaped association between DBP and the composite cardiovascular outcome \( (P \text{ nonlinearity}=0.002) \). The pattern was similar in both the intensive and standard treatment strategy groups \( (P \text{ interaction}=0.75; \text{ Figure S2, right}) \). The hazard increased when DBP was >85 or <55 mm Hg. When considering diastolic pressure as a categorical variable, the HRs of DBP <55 and >90 mm Hg relative to DBP between 55 and 90 mm Hg were 1.52 (95% CI, 0.99–2.34) and 0.95 (95% CI, 0.37–2.40), respectively. Of note, a similar J-shaped relationship in the primary outcome was observed when CVD and non-CVD patients were combined \( (P \text{ nonlinearity}<0.0001) \).

Figure 2. Association between diastolic blood pressure (DBP) and the composite cardiovascular outcome according to history of cardiovascular disease (CVD). Hazard ratios and 95% confidence intervals of the composite cardiovascular outcome for a range of follow-up diastolic pressure \( \text{ (left, for subjects without history of CVD and right for patients with CVD)} \). Model was adjusted for treatment arm, baseline systolic blood pressure (SBP), follow-up SBP, age, sex, body mass index, Framingham 10-year risk score, estimated glomerular filtration rate.
the individual end points of MI and heart failure (Table S1; Figures S4 through S6).

**Predictors of Low DBP (<55 mm Hg)**

As seen in Figure 3, a greater proportion of visits fell <55 mm Hg in the intensive arm (9.22%) than the standard arm (3.42%).

A lower baseline DBP increased the odds, whereas a higher baseline SBP with a low DBP (widened pulse pressure) increased the odds of the DBP falling <55 mm Hg (Figure S7). Other baseline predictors are presented in Table 3 (and by treatment Table S2). There was also an interaction between treatment and study duration ($P_{interaction}<0.001$). Odds ratio of intensive versus standard was 4.42 (95% CI, 3.87–5.04) at 6 months, increasing to 6.24 (95% CI, 5.50–7.08) at 2 years.

**Discussion**

This study demonstrated a J-shaped relationship between DBP and risk of increased cardiovascular events <55 and >95 mm Hg. This pattern was similarly observed in the SPRINT patient population with a history of clinical CVD but at an upper diastolic threshold of 85 mm Hg. When taking account of DBP, there was no evidence of a J-shaped relationship between follow-up SBP and cardiovascular risk. Predictors of achieving a diastolic pressure of $\leq 55$ mm Hg included lower baseline diastolic pressure <70 mm Hg, higher baseline SBP when accompanied by a low baseline DBP, male sex, older age, history of CVD, and elevated baseline creatinine.

Many observational studies and post hoc analyses of achieved BP in randomized controlled trials demonstrated a J- or U-shaped relationship between DBP and various cardiovascular outcomes. However, the nadir diastolic pressures from these studies were considerably higher than identified in our analysis and generally ranged from 70 to 85 mm Hg. Further, studies predominantly identified a J curve in patients with coronary disease. Our analysis identified a J-curve relationship with follow-up diastolic pressure in those with and without CVD <55 mm Hg. The CLARIFY international cohort study (The Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease) and INVEST study (The International Verapamil-Trandolapril Study) of patients with stable coronary disease found that cardiovascular risk doubled when DBP was <60 and 70 mm Hg, respectively. The SYST-EUR trial (Systolic Hypertension in Europe) of 4695 elderly persons targeted an SBP to <150 mm Hg and also demonstrated a J curve for diastolic pressure <70 mm Hg but only in patients with coronary disease. However, in INVEST and other trials, the target BP in patients without diabetes mellitus was <140/90 mm Hg so achieving a diastolic pressure of <70 mm Hg may have been attributed to reverse causation or arterial stiffness and widened pulse pressure. The HOT trial (Hypertension Optimal Treatment), unlike previous trials, did prospectively target lowering DBP to $\leq 80$, $\leq 85$, and $\leq 90$ mm Hg. The HOT trial also demonstrated an increase in MI only with diastolic pressures <80 mm Hg in the subset of patients with coronary disease. The reasons for the higher DBP thresholds identified in previous analyses compared with our current analysis may be because of trial procedural differences. The baseline diastolic pressure in these earlier studies were considerably higher than in the SPRINT study, ranging from $\approx 85$ mm Hg in INVEST and SYST-EUR to 105 mm Hg in the HOT trial. Of note, the delta change in DBP of 25 mm Hg in the HOT trial associated with increased cardiovascular risk was analogous to our reduction of 23 mm Hg also associated with increased cardiovascular risk. The SPRINT trial used a mean of 3 unattended fully automated BP measurements, whereas other studies used casual office readings or a mean of 2 seated attended BPs measured by research staff using oscillometric or auscultatory methods. The difference in BPs between such methods can be 5 to 10 mm Hg lower with the unattended BP measures and unattended fully automated oscillometric measure compared with manual office BP readings or readings conducted when others are present or
diovascular risk decreased with decreasing systolic pressure. In an analysis of the SBP was 119 mm Hg.

Table 3. OR and 95% CIs of Baseline Factors for Falling Below a DBP of 55 mm Hg

<table>
<thead>
<tr>
<th>Baseline Factors</th>
<th>OR (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study duration (per year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>1.07 (1.02–1.12)</td>
<td>0.011</td>
</tr>
<tr>
<td>Intensive</td>
<td>1.35 (1.30–1.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline DBP (per 10 mmHg increase)</td>
<td>0.20 (0.19–0.21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline SBP (per 10 mm Hg increase)</td>
<td>1.80 (1.72–1.88)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (per 10 yr increase)</td>
<td>1.67 (1.54–1.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>1.22 (1.06–1.39)</td>
<td>0.005</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>1.43 (1.24–1.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine (per 2-fold increase)</td>
<td>1.20 (1.03–1.39)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Smoke (reference: Never)

<table>
<thead>
<tr>
<th>Race (reference: Non-Hispanic white)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic black</td>
<td>0.88 (0.76–1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.85 (0.70–1.03)</td>
<td>0.09</td>
</tr>
<tr>
<td>Other</td>
<td>1.08 (0.73–1.61)</td>
<td>0.70</td>
</tr>
<tr>
<td>Body mass index (per 10 kg/m² increase)</td>
<td>0.96 (0.86–1.07)</td>
<td>0.42</td>
</tr>
<tr>
<td>Triglycerides (per 2-fold increase)</td>
<td>1.02 (0.94–1.11)</td>
<td>0.64</td>
</tr>
<tr>
<td>Cholesterol (per 40 mg/dL increase)</td>
<td>0.96 (0.90–1.02)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

DBP indicates diastolic blood pressure; and OR, odds ratio.

*Based on a multivariate logistic regression with random intercepts. Out of 119,384 visits from 9078 participants who contributed to the analysis, 7573 follow-up DBPs from 2350 patients were <55 mm Hg.

Few studies examining the J-curve phenomena also evaluated the combined effect of lowering SBP and DBP on cardiovascular outcomes. The INVEST study identified that the nadir of SBP was 119 mm Hg and the CLARIFY cohort identified an increased risk of CV events below a systolic pressure of 120 mm Hg. The J curve for the systolic pressure was less evident compared with the DBP curve, an observation similar to our analysis. Our findings of additional linear benefit of lowering systolic pressure after adjusting for diastolic pressure in those with CVD also confirm previous findings. In an analysis of the Framingham data, evaluation of both systolic and diastolic pressures better predicted future cardiovascular events compared with either alone. After adjusting for diastolic pressure, cardiovascular risk decreased with decreasing systolic pressure.

The pathophysiologic underpinnings of the J- or U-shaped relationship between diastolic pressure and CVD risk are likely multifold. DBP is a major determinant of coronary blood flow as coronary perfusion occurs during diastole. As noted, we observed a J-shaped relationship between MI and heart failure and low achieved diastolic pressure. Also, the J- or U-shaped relationship may result from arterial stiffness reflected in a widened pulse pressure and impaired coronary perfusion as the retrograde aortic wave returns during late systole rather than diastole, leading to increased cardiovascular risk. Patients in the SPRINT trial may have had more arterial stiffness given their advanced age and high prevalence of chronic kidney disease even among those without documented CVD. Other confounding factors such as heart failure, malnutrition, or malignancy may also contribute to the J-shaped relationship between low diastolic pressure and the composite cardiovascular events. Although heart failure patients were excluded from SPRINT, in a mediation analysis using SPRINT data, Stensrud and Strohmair determined that confounding factors played an indirect or direct role in the J-shaped relationship. However, this analysis did not include data from the first year of the study. Our findings using the totality of data adjusting for multiple confounders demonstrated a J curve with individual end points of MI, heart failure, and our composite cardiovascular outcome.

The strengths of this analysis include accurate measurement of BP using unattended automated BP measures, use of data from a large clinical trial with prospective intensive low BP targets that allow further exploration of lower diastolic pressure and CVD risk, and the inclusion of elderly patients with and without a history of clinical CVD. However, there are several limitations to note. First, DBPs were not explicitly targeted in the SPRINT trial. As such, very low achieved diastolic pressures may reflect some reverse causation that we were not able to eliminate. We observed that patients with achieved DBP <55 mm Hg were associated with higher baseline cardiovascular risk burden than patients who did not have follow-up DBP <55 mm Hg (Table 3). However, mean follow-up diastolic and systolic pressures in this study were considerably lower in SPRINT compared with earlier studies. There may be residual confounding where we were unable to account for issues of malnutrition or malignancy that may have distorted the relationship between low DBP and outcomes. Further, there may be target organ heterogeneity where lower BP may have differential effects on cardiac end points compared with stroke end points. When we additionally analyzed total mortality, the threshold of diastolic pressure was generally unchanged. This analysis did not include other end points such as emergency department visits for hypotension, acute kidney injury, or injurious falls that may occur at very low diastolic pressures as well. Finally, the seated BP measurements used in SPRINT, unattended fully automated devices, may differ from some clinician offices, and therefore, the results of this analysis may not be generalized when using other BP measurement techniques.

**Perspectives**

In conclusion, intensive BP lowering in patients who have hypertension, but do not have diabetes mellitus, stroke, or heart failure, may increase cardiovascular risk if the diastolic pressure falls to ≤55 mm Hg. Although the observed J-shaped relationship might be because of reverse causality, we advise that clinicians should use caution when trying to achieve SPRINT intensive targets especially among those at risk including men,
older patients, those with CVD, those with low baseline diastolic pressure, and those with elevated creatinine. These data also suggest that there is a group of patients with CVD, perhaps those with effective myocardial reperfusion, in whom DBP lowering does not produce a greater risk than persons without CVD when DBP is measured as <60 mm Hg using unattended, fully automated BP devices with proper measurement technique.

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Disclosures
None.

References

Novelty and Significance
What Is New?
• This J-curve analysis used large trial data of at-risk persons without diabetes mellitus where intensively low blood pressure was prospectively targeted.
• This is the first J-curve analysis study where the blood pressures were measured using unattended, fully automated blood pressure measures.

What Is Relevant?
• There is significant concern among care providers that while targeting intensive systolic targets, cardiovascular risk may increase below some threshold of diastolic pressure. These results identify a threshold and predictors for increased risk.

Summary
In the SPRINT (Systolic Blood Pressure Intervention Trial) population, a diastolic threshold of <55 mm Hg was associated with increased cardiovascular events in both patients with and without cardiovascular disease—a lower diastolic threshold than observed in earlier analyses where intensively low blood pressures were not targeted.
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Data Supplement

Effect of Lowering Diastolic and Systolic Blood Pressure in Patients with and without Prior Cardiovascular Disease: Analysis of the SPRINT trial

Short title: Intensive Blood Pressure Lowering in the SPRINT trial: How low is too low?

Nadia A KHAN, MD, MSc\textsuperscript{a}, Simon W RABKIN MD\textsuperscript{b}, Yinshan ZHAO PhD\textsuperscript{c}, Finlay A MCALISTER MD, MPH\textsuperscript{d}, Julie E PARK MMath\textsuperscript{c}, Meijiao GUAN PhD\textsuperscript{c}, Sammy CHAN MD\textsuperscript{b}, Karin H HUMPHRIES DSc\textsuperscript{b,c}

\textsuperscript{a} Division of Internal Medicine, Department of Medicine, and Center for Health Evaluation and Outcomes Science, University of British Columbia, Vancouver, BC, Canada
\textsuperscript{b} Division of Cardiology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada
\textsuperscript{c} British Columbia Centre for Improved Cardiovascular Health, Vancouver, BC, Canada
\textsuperscript{d} Division of Internal Medicine, Department of Medicine, University of Alberta, Edmonton, AB, Canada

Address for correspondence:
Nadia Khan MD MSc
540.70, 1081 Burrard Street,
Vancouver, BC, V6Z 1Y6
P:604 353-7548
F:604 806-8005
Email: nakhanubc@gmail.com

Co-author email addresses: simon.rabkin@ubc.ca, Finlay.McAlister@ualberta.ca, yinshans@providencehealth.bc.ca, SChan@providencehealth.bc.ca, jpark@icvhealth.ubc.ca, mguan@icvhealth.ubc.ca
Data Supplement

1. Interaction by sex and follow up DBP for the primary outcome

In the cohort without CVD, the adjusted hazard in women was relatively higher than in men, although not significant (HR: 1.30, 95% CI: 0.95 to 1.78). The interaction between follow-up DBP and sex was not significant (p-value = 0.78) indicating a similar J-shaped association regardless sex.

In the cohort with CVD, the adjusted hazard in women was significantly higher in men (HR: 1.61, 95% CI: 1.05 to 2.47). The interaction between follow-up DBP and sex was not significant (p-value = 0.28).

2. Interaction by age (≥ 75 vs. < 75) and follow up DBP for the primary outcome

We investigated whether the J shaped association of follow up DBP differs by age (≥ 75 years and < 75 years). We found a significant interaction between age and follow-up DBP (p-interaction = 0.004) in the cohort without CVD, but not in the cohort with CVD (p-interaction = 0.13). When plotted by age (≥ 75 vs. < 75) (Figure S3), the elevation of hazard at low DBP was apparent in both age groups from the cohort without CVD. There was also an elevation of the hazard in those ≥ 75 years age in the cohort with CVD, however the elevation was not evident in the younger patients of this cohort.
Table S1. Test of significance of nonlinearity in follow up DBP for individual endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Without history of CVD Cohort</th>
<th>With history of CVD</th>
<th>P value for nonlinearity</th>
<th>P value for nonlinearity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events (N)</td>
<td>Events (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>126</td>
<td>74</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke</td>
<td>88</td>
<td>33</td>
<td>0.18</td>
<td>0.72</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>97</td>
<td>49</td>
<td>0.02</td>
<td>0.008</td>
</tr>
</tbody>
</table>
### Table S2. Odds ratio (OR) and 95% confidence intervals (CIs) of baseline factors for falling below a DBP of 55 mmHg according to treatment

<table>
<thead>
<tr>
<th>Baseline factors</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard arm</td>
</tr>
<tr>
<td>Study Duration (per year)</td>
<td>1.07 (1.02, 1.13)</td>
</tr>
<tr>
<td>Baseline DBP (per 10 mmHg increase)</td>
<td>0.20 (0.17, 0.22)</td>
</tr>
<tr>
<td>Baseline SBP (per 10 mmHg increase)</td>
<td>1.76 (1.63, 1.90)</td>
</tr>
<tr>
<td>Age (per 10 years increase)</td>
<td>1.82 (1.57, 2.10)</td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
<td>0.91 (0.71, 1.16)</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>1.45 (1.14, 1.86)</td>
</tr>
<tr>
<td>Creatinine (per two-fold increase)</td>
<td>1.43 (1.09, 1.86)</td>
</tr>
<tr>
<td>Smoke (reference: Never)</td>
<td>1.22 (0.98, 1.51)</td>
</tr>
<tr>
<td>Former</td>
<td>1.22 (0.79, 1.88)</td>
</tr>
<tr>
<td>Current</td>
<td></td>
</tr>
<tr>
<td>Race (reference: Non-Hispanic white)</td>
<td>0.83 (0.63, 1.09)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>0.73 (0.51, 1.05)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.12 (0.52, 2.40)</td>
</tr>
<tr>
<td>Other</td>
<td>0.92 (0.75, 1.14)</td>
</tr>
<tr>
<td>Body mass index (per 10 kg/m² increase)</td>
<td>1.05 (0.90, 1.23)</td>
</tr>
<tr>
<td>Triglycerides (per two-fold increase)</td>
<td>0.91 (0.81, 1.02)</td>
</tr>
<tr>
<td>Cholesterol (per 40 mg/dl increase)</td>
<td></td>
</tr>
</tbody>
</table>

*Based on a multivariate logistic regression with random intercepts. In Standard arm, out of 59,118 visits from 4,518 participants that contributed to the analysis, 2,023 follow-up DBPs from 753 participants were below 55 mmHg. In Intensive arm, out of 60,266 visits from 4,560 participants, 5,550 follow-up DBPs from 1,610 participants were below 55 mmHg.
Figure S1. Hazard ratios and 95% CIs for the primary outcome by treatment arm over a range of follow-up SBP in the cohort without cardiovascular disease. The references hazard ratios were standard treatment arm with both baseline SBP and follow-up SBP at 140 mmHg. The model was adjusted for treatment arm, baseline SBP, follow-up SBP, age, sex, body mass index, Framingham 10 year risk score, and eGFR. The references hazard ratios were standard treatment arm with both baseline SBP and follow-up SBP at 140 mmHg. The p value for nonlinearity was 0.03.
Figure S2. Hazard ratios and 95% confidence intervals of the composite cardiovascular outcome for a range of follow-up diastolic blood pressure by CVD cohort and treatment arm. All models were adjusted for treatment arm, baseline SBP, follow-up SBP, age, sex, body mass index, Framingham 10 year risk score, and eGFR.
Figure S3. Hazard ratios and 95% confidence intervals of the composite cardiovascular outcome for a range of follow-up diastolic blood pressure by CVD cohort and age group. All models were adjusted for treatment arm, baseline SBP, follow-up SBP, age, sex, body mass index, Framingham 10 year risk score, and eGFR.
Figure S4. Hazard ratios and 95% confidence intervals of myocardial infarction for a range of follow-up diastolic pressure. All models were adjusted for treatment arm, baseline SBP, follow-up SBP, age, sex, body mass index, Framingham 10 year risk score, and eGFR.
Figure S5. Hazard ratios and 95% confidence intervals of heart failure for a range of follow-up diastolic pressure. All models were adjusted for treatment arm, baseline SBP, follow-up SBP, age, sex, body mass index, Framingham 10 year risk score, and eGFR.
Figure S6. Hazard ratios and 95% confidence intervals of stroke for a range of follow-up diastolic pressure. All models were adjusted for treatment arm, baseline SBP, follow-up SBP, age, sex, body mass index, Framingham 10 year risk score, and eGFR.
Figure S7. Estimated probability of having a follow-up DBP < 55mmHg at a range of baseline DBP values. Based on the multivariable logistic regression and evaluated at 1 year post baseline for a never smoked non-Hispanic white male without a history of CVD and with cohort averages of all the continuous predictors (age, BMI, baseline SBP, log triglycerides, log cholesterol and log creatinine).