Orthostatic Hypotension, Cardiovascular Outcomes, and Adverse Events

Results From SPRINT

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Abstract—Orthostatic hypotension (OH) is frequently observed with hypertension treatment, but its contribution to adverse outcomes is unknown. The SPRINT (Systolic Blood Pressure Intervention Trial) was a randomized trial of adults, age ≥50 years at high risk for cardiovascular disease with a seated systolic blood pressure (BP) of 130 to 180 mm Hg and a standing systolic BP ≥110 mm Hg. Participants were randomized to a systolic BP treatment goal of either <120 or <140 mm Hg. OH was defined as a drop in systolic BP ≥20 or diastolic BP ≥10 mm Hg 1 minute after standing from a seated position. We used Cox models to examine the association of OH with cardiovascular disease or adverse study events by randomized BP goal. During the follow-up period (median 3years), there were 1170 (5.7%) instances of OH among those assigned a standard BP goal and 1057 (5.0%) among those assigned the intensive BP goal. OH was not associated with higher risk of cardiovascular disease events (primary outcome: hazard ratio 1.06 [95% CI, 0.78–1.44]). Moreover, OH was not associated with syncope, electrolyte abnormalities, injurious falls, or acute renal failure. OH was associated with hypotension-related hospitalizations or emergency department visits (hazard ratio, 1.77 [95% CI, 1.11–2.82]) and bradycardia (hazard ratio, 1.94 [95% CI, 1.19–3.15]), but these associations did not differ by BP treatment goal. OH was not associated with a higher risk of cardiovascular disease events, and BP treatment goal had no effect on OH's association with hypotension and bradycardia. Symptomless OH during hypertension treatment should not be viewed as a reason to down-titrate therapy even in the setting of a lower BP goal.

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Orthostatic hypotension (OH), a drop in blood pressure (BP) after standing, is common among older adults[1] and has been reported to be an important predictor of falls, syncope, cardiovascular disease (CVD), and death.[1–3] OH is highly prevalent among older adults with hypertension[4] and in the setting of hypertension treatment.[5] These observations have contributed to concerns that aggressive BP lowering, especially in older adults, might increase OH and its sequelae.

Recently, SPRINT (Systolic Blood Pressure Intervention Trial) demonstrated that a lower systolic BP (SBP) treatment

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goal reduced the risk of CVD events and total mortality in middle-aged and older adults without diabetes mellitus when compared with conventional goals.[6] SPRINT also found that the lower BP target reduced risk of OH, despite increasing risk of hypotension and possibly syncope without increasing injurious falls.[7] It was later shown that CVD risk factors were associated with OH[8] and that baseline OH in SPRINT was associated with falls,[7] but whether OH identified during the post-randomization period, overall or with intensive BP intervention, was related to CVD or adverse events has not been reported.

Our objectives were to determine (1) the association of OH with CVD or adverse events and (2) whether OH detected in the setting of intensive hypertension treatment was associated with greater risk of events than OH detected in the setting of standard BP treatment goal. We hypothesized that OH would be associated with CVD and adverse events and that OH in the setting of an intensive BP treatment goal would be associated with a higher risk of CVD and adverse events.

Methods

The data that support the findings of this study are available from the National Heart, Lung, and Blood Institute BioLINCC repository.

SPRINT was a National Institutes of Health–funded, prospective, randomized, controlled, and open-label outcome trial with blinded end point determination conducted at 102 clinical sites throughout the United States and Puerto Rico between November 2010, and August 2015.[6,9,10] The trial compared intensive treatment to a SBP target <120 mm Hg and standard treatment to a SBP target <140 mm Hg. Institutional Review Boards at each site approved the original protocol, including subsequent analyses. All participants provided written informed consent. This analysis is based on SPRINT's final expanded data set.

Participants

SPRINT recruited adults (≥50 years) with a SBP of 130 to 180 mm Hg and a high-CVD risk based on CVD history, chronic kidney disease (CKD) with estimated glomerular filtration rate of 20 to 59 mL/(min·1.73 m^2), or 10-year Framingham Risk Score ≥15%. The study enhanced recruitment of adults aged ≥75 years, with CKD, and blacks. Nursing home residents or persons with diabetes mellitus, prior stroke, dementia, symptomatic or severe heart failure (or measured left ventricular ejection fraction <35%), or a 1-minute standing SBP <110 mm Hg were excluded. Of the original 9361 participants, 569 were excluded due to a missing covariate of interest at baseline.

Intervention

Participants were randomly assigned to either intensive or standard hypertension treatment. Over the first 3 months, visits occurred monthly. Afterward, visits occurred every 3 months. Among the intensive group, participant visits continued monthly until SBP was <120 mm Hg or the investigator decided not to intensify further. Titration of antihypertensive therapy was based on BP measurements at each visit. All major classes of antihypertensive medications were available to target a SBP of <120 mm Hg (intensive) or a SBP between 135 and 139 mm Hg (standard). Among those assigned the standard treatment, antihypertensive medications were reduced if SBP was <130 mm Hg on a single visit or <135 mm Hg on 2 consecutive visits.

Orthostatic Hypotension

OH was assessed at screening, baseline, 1-month, 6-month, 12-month, and then yearly visits. While there was no exclusion for history of OH, during the screening visit, adults with a 1-minute standing SBP <110 mm Hg were excluded from participation. Seated BP was measured 3× after a 5-minute quiet rest, using an automated, oscillometric sphygmomanometer (Omron 907XL, Omron Healthcare, Lake Forest, IL). Participants were then instructed to stand, and after 1 minute BP was remeasured.[8,11] OH was defined as a difference in standing and mean sitting SBP ≥20 mm Hg or diastolic BP ≥10 mm Hg. Participants completing the standing BP exam were further asked about dizziness; however, we did not differentiate between dizziness status due to small numbers (Table 1, Table S1 in the online-only Data Supplement). OH detected during the randomization visit before starting the trial intervention was considered baseline OH, while OH detected after randomization during follow-up visits was considered post-randomization OH.

Study Outcomes

The primary outcome combined the first episode of myocardial infarction, nonmyocardial infarction acute coronary syndrome (ACS), stroke, acute decompensated heart failure, or death from cardiovascular causes. The individual components of the primary outcome or all-cause mortality were secondary. All outcomes were adjudicated by a committee blinded to treatment assignment.

Study Adverse Events

At each visit, staff asked participants about hospitalizations, emergency department visits, and adverse events. The following expected

Table 1. Baseline Characteristics, Overall and by Baseline Orthostatic Hypotension Status

	Overall (N=8792)	No Baseline OH (N=8156)	Baseline OH (N=636)
Age, y	67.6 (9.3)	67.5 (9.3)	69.4 (9.3)
Age ≥75 y, %	26.9	26.3	34.6
Female, %	35.0	34.6	40.9
Black, %	31.3	31.9	23.7
Mean SBP, mm Hg	139.6 (15.6)	139.1 (15.5)	145.2 (16.5)
Mean DBP, mm Hg	78.2 (11.9)	78.1 (11.9)	79.9 (12.3)
eGFR, mL·min/1.73 m^2	72.2 (20.4)	72.6 (20.2)	66.3 (21.3)
Body mass index, kg/m^2	29.9 (5.8)	30.0 (5.8)	29.2 (5.6)
HDL cholesterol, mg/dL	52.8 (14.4)	52.7 (14.4)	53.4 (14.2)
Total cholesterol, mg/dL	187.0 (42.5)	187.1 (42.4)	185.3 (43.5)
Statin use, %	43.3	43.0	48.0
Chronic kidney disease, %	27.4	26.4	40.1
Subclinical or clinical CVD, %	19.9	19.7	22.3
Smoking status, %			
Never	43.8	44.0	42.0
Former	42.8	42.6	45.6
Current	13.4	13.5	12.4
No. of hypertensive agents prescribed at baseline, %			
0	9.1	9.1	8.2
1	34.8	34.9	33.0
2	34.0	34.1	33.6
3	17.9	17.6	21.1
≥4	4.2	4.2	4.1
Self-reported dizziness with standing, %*	4.3	4.2	5.5

Total N for those reporting dizziness was 8791/8155/636. CVD indicates cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; OH, orthostatic hypotension; and SBP, systolic blood pressure.

*Dizzy status was missing for 1 person

events were specifically collected by investigators to monitor safety: hypotension, syncope, injurious falls, electrolyte abnormalities, bradycardia, and acute kidney injury or acute renal failure. A hypotension event was based on mention of symptomatic low BP (without specific BP cut-offs) in admission history and physicals or discharge summaries of hospitalization records.[7] The definition of an injurious fall was a fall resulting in an emergency department evaluation or a hospitalization. A bradycardia event was based on the mention of symptomatic low heart rate in hospitalization records.

Other Covariate Measurements and Definitions

Age, sex, race, smoking status (never, former, current), baseline statin use, and antihypertension medication use were ascertained via self-report; estimated glomerular filtration rate was determined using the 44 variable Modification of Diet in Renal Disease equation based on serum creatinine assessments. CKD was defined as an estimated glomerular filtration rate <60 mL/(min·1.73 m^2). Body mass index was derived from standardized measurements of height and weight. HDL (high-density lipoprotein) cholesterol and total cholesterol were measured in serum using standard assays. Diagnosis of subclinical or clinical CVD was based on a combination of self-report, prior studies, and documentation of CVD or CVD equivalent events.[6,9,10]

Statistical Analysis

Study population characteristics were described using means (SD) and proportions overall and according to baseline OH status. We also determined the prevalence of OH at baseline and at each follow-up visit. We used Poisson regression, adjusted for BP target assignment, age, sex, and race, to estimate incidence rates overall and by baseline OH status.

Cox proportional hazards models stratified by clinic site were used to examine the association of OH as a time-varying covariate detected at baseline or during post-randomization visits with the trial's primary and secondary outcomes and serious adverse events. Models were adjusted for age, sex, race, and treatment assignment (model 1). In a second model (model 2), we adjusted for the following baseline covariates: age, sex, race, treatment assignment, SBP, diastolic BP, body mass index, HDL cholesterol, total cholesterol, statin use, CKD, estimated glomerular filtration rate, subclinical or clinical CVD, smoking status, and number of hypertensive medications. Both models were stratified by research site. For these analyses, participants were censored when an event occurred or at the end of follow-up if no event occurred.

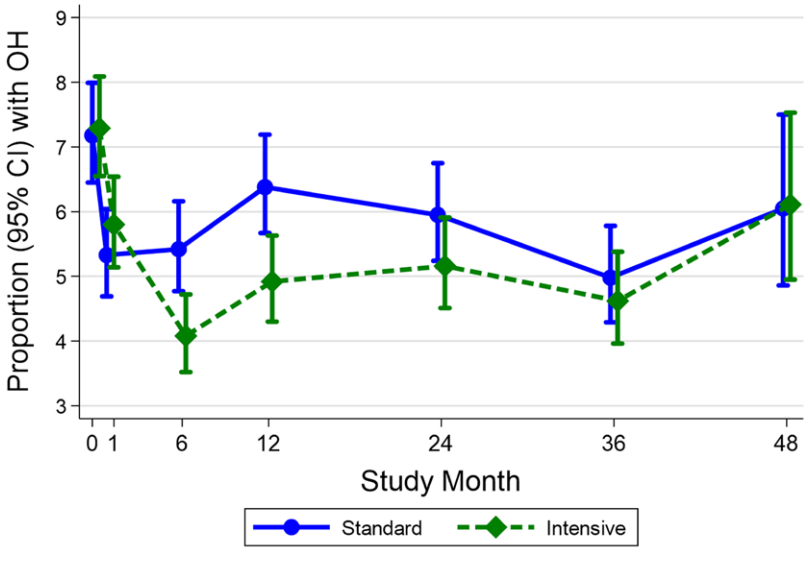
We also examined the association of time-varying OH detected during the follow-up period (post-randomization OH only) with trial outcomes and adverse events by randomized BP goal assignment to isolate the effects of treatment on OH. Models were stratified by research site and adjusted for the covariates in model 2 above along with baseline OH. We used interaction terms to compare associations across BP goal assignments.

Analyses were conducted with Stata v15.1 (StataCorp, College Station, TX). *P* values were 2-sided and not adjusted for multiple comparisons.

Results

Baseline characteristics of the 8792 SPRINT participants included in our analysis are shown overall and by baseline OH status in Table 1. Overall, the mean age of participants was 67.6±9.3 years; 35.0% were female, and 31.3% were black. The mean baseline SBP was 139.6±15.6 mm Hg, and the mean baseline diastolic BP was 78.2±11.9 mm Hg; 636 participants had OH at baseline (Figure).

During a median of 3.0 years of post-randomization follow-up, there were 2227 instances of OH, representing 1627 (18.5% of 8792) participants. The distribution of change in BP was similar across baseline, intensive, and standard treatment



N with an OH assessment at each visit

BP Goal	0	1	6	12	24	36	48
Standard							
No OH	4058	4034	3875	3739	3559	3110	1196
OH	314	227	222	255	225	163	77
Total	4372	4261	4097	3994	3784	3273	1273
Intensive							
No OH	4098	4060	3998	3845	3654	3221	1260
OH	322	250	170	199	199	156	82
Total	4420	4310	4168	4044	3853	3377	1342

Figure. The proportion with orthostatic hypotension (OH) during the trial and number of participants contributing to OH assessments by treatment assignment. BP indicates blood pressure.

visits (Figure S1). In both treatment groups, the visit with the higher proportion of OH was the baseline visit (>7% versus <6.5% during post-randomization visits). Furthermore, OH was more common among those assigned standard treatment at most visits over the course of the trial compared with those assigned intensive treatment (Figure).

In both treatment groups combined, OH detected during baseline or follow-up was not associated with the primary outcome (adjusted hazard ratio [HR] of 1.06 [95% CI, 0.78–1.44]) or any secondary outcomes (Table 2, Table S2). With regard to serious adverse events, OH was only associated with hypotension events (HR, 1.77 [95% CI, 1.11–2.82]) and bradycardia (HR, 1.94 [95% CI, 1.19–3.15]; Table 3).

The association of post-randomization OH with trial outcomes and serious adverse events by BP goal assignment is shown in Table 4. There was evidence of a higher hazard for nonmyocardial infarction ACS among participants assigned the intensive BP goal versus the standard BP goal (HR, 2.56 [95% CI, 1.04–6.31] for intensive versus 0.35 [95% CI, 0.05–2.73] for standard; *P* interaction=0.03; see Table S3). After adjustment, OH was associated with hypotension events among those assigned the standard BP goal (HR, 3.26 [95% CI, 1.56–6.81]) but not among those assigned the intensive goal (HR, 1.35 [95% CI, 0.71–2.59]); however, the interaction did not achieve statistical significance.

Discussion

In this cohort of hypertensive, middle-aged and older adults, we found that OH did not predict CVD events. Although OH was associated with hypotension and bradycardia, these associations did not differ by randomized treatment group. Aside from nonmyocardial infarction ACS, associations between OH and CVD outcomes or adverse events (including hypotension and bradycardia events) did not differ by assigned BP target.

OH was present in about 7% of participants at baseline and in <7% of participants through follow-up. Other BP trials have reported a baseline prevalence of OH between 3% and 17%.[12–16] OH is a manifestation of BP dysregulation on change in position. While traditionally viewed as a neurogenic condition, emerging evidence suggests that CVD may also represent a common cause of OH.[17] This relationship was observed in a previously published analysis of SPRINT baseline characteristics and postural change in BP where a number of CVD risk factors, including age, CKD, and smoking were associated with larger reductions in standing BP.[8] Moreover, both the primary SPRINT publication and the present study showed that intensive treatment of hypertension, a CVD risk factor, lowered risk of OH.[6] This is despite the greater number of antihypertensive medications and greater use of diuretics (chlorthalidone) in the intensive arm.[6] This suggests that CVD may represent an important contributor to OH.

Whether OH contributes to CVD events remains controversial. Multiple studies have observed that OH is a predictor of CVD events,[1,3,17–20] leading to the hypothesis that transient hypoperfusion of the heart from OH contributes to cumulative micro-ischemia over time.[21–23] However, this relationship has not been observed in all studies[24–26] and was not observed

Table 2. Adjusted* Incidence Rates (Per 10 000 Person-Years) of Trial Outcomes or Serious Adverse Events, Overall and by Baseline Orthostatic Hypotension Status

	Overall		No Baseline OH		Baseline OH	
	Event/No Event	IR (95% CI)	Event/No Event	IR (95% CI)	Event/No Event	IR (95% CI)
Outcomes						
Primary outcome	649/8089	5.7 (5.2–6.1)	588/7515	5.6 (5.2–6.1)	61/574	5.8 (5.4–6.2)
Secondary outcomes						
Myocardial infarction	246/8495	2.2 (2.0–2.5)	225/7881	2.2 (2.0–2.5)	21/614	2.3 (2.1–2.6)
Acute coronary syndrome	84/8659	0.8 (0.7–1.0)	72/8036	0.9 (0.7–1.0)	12/623	0.8 (0.6–1.0)
Stroke	156/8590	1.6 (1.3–1.8)	141/7970	1.6 (1.3–1.8)	15/620	1.7 (1.5–1.9)
Heart failure	187/8555	1.5 (1.2–1.8)	172/7935	1.5 (1.2–1.8)	15/620	1.7 (1.4–1.9)
Death from cardiovascular causes	122/8624	0.8 (0.7–1.0)	111/8000	0.8 (0.7–1.0)	11/624	0.9 (0.7–1.1)
Death from any cause	364/8381	2.6 (2.3–2.9)	322/7788	2.6 (2.3–2.8)	42/593	2.8 (2.5–3.0)
Primary outcome or death	856/7880	5.5 (5.2–5.9)	774/7327	5.5 (5.1–5.9)	82/553	5.6 (5.3–6.0)
Serious adverse events						
Hypotension	220/8562	2.4 (2.1–2.7)	201/7945	2.4 (2.1–2.7)	19/617	2.4 (2.1–2.7)
Syncope	247/8539	2.3 (2.1–2.6)	227/7923	2.3 (2.1–2.6)	20/616	2.5 (2.2–2.8)
Bradycardia	176/8610	1.7 (1.4–2.0)	154/7997	1.7 (1.4–2.0)	22/613	1.9 (1.6–2.2)
Electrolyte abnormality	298/8488	2.8 (2.5–3.1)	269/7881	2.8 (2.5–3.1)	29/607	3.0 (2.7–3.3)
Injurious fall	654/8122	5.5 (5.0–6.0)	590/7551	5.4 (5.0–5.9)	64/571	6.4 (5.9–6.8)
Acute kidney injury or acute renal failure	317/8465	2.7 (2.4–3.0)	294/7853	2.7 (2.4–3.0)	23/612	2.7 (2.5–3.0)

Total number varies by outcome or serious adverse event depending on whether orthostatic hypotension assessments were missing before the outcome or serious adverse event occurred. IR indicates incidence rate; and OH, orthostatic hypotension.

*Adjusted for blood pressure assignment, age, sex, and race.

Table 3. Association of Orthostatic Hypotension as Time-Varying Covariate Detected During Baseline or Post-Randomization Follow-Up With Trial Outcomes, N=8792

	Total no. of Events	Orthostatic Hypotension (Model 1)		Orthostatic Hypotension (Model 2)	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Outcomes					
Primary outcome	649	1.16 (0.85–1.57)	0.36	1.06 (0.78–1.44)	0.72
Secondary outcomes					
Myocardial infarction	246	0.97 (0.57–1.66)	0.92	0.92 (0.54–1.58)	0.77
Acute coronary syndrome	84	1.87 (0.91–3.83)	0.09	1.68 (0.81–3.49)	0.16
Stroke	156	0.95 (0.47, 1.91)	0.89	0.86 (0.43–1.73)	0.68
Heart failure	187	1.09 (0.63–1.88)	0.76	0.96 (0.55–1.68)	0.89
Death from cardiovascular causes	122	0.73 (0.32–1.69)	0.46	0.63 (0.27–1.47)	0.29
Death from any cause	364	1.24 (0.84–1.83)	0.29	1.13 (0.76–1.68)	0.53
Primary outcome or death	856	1.20 (0.92–1.56)	0.17	1.11 (0.85–1.44)	0.46
Serious adverse events					
Hypotension	220	1.99 (1.26–3.14)	0.003	1.77 (1.11–2.82)	0.02
Syncope	247	1.49 (0.93–2.39)	0.10	1.38 (0.86–2.23)	0.18
Bradycardia	176	2.10 (1.30–3.39)	0.002	1.94 (1.19–3.15)	0.008
Electrolyte abnormality	298	1.08 (0.66–1.75)	0.76	0.99 (0.60–1.62)	0.97
Injurious fall	654	1.24 (0.91–1.68)	0.17	1.20 (0.88–1.63)	0.24
Acute kidney injury or acute renal failure	317	1.35 (0.86–2.13)	0.20	1.14 (0.72–1.81)	0.58

Model 1: adjusted for age, sex, race. Model 2: adjusted for age, sex, race and the following baseline characteristics: treatment assignment, systolic blood pressure, diastolic blood pressure, body mass index, high-density lipoprotein cholesterol, total cholesterol, statin use, chronic kidney disease, estimated glomerular filtration rate, subclinical or clinical cardiovascular disease, smoking status, or number of hypertensive medications. Stratified by research site. Orthostatic hypotension is defined by consensus as a drop in systolic blood pressure ≥20 mm Hg or as a drop in diastolic blood pressure ≥10 mm Hg. In SPRINT, a serious adverse event was defined as events that (1) were fatal or life-threatening, (2) resulted in clinically significant or persistent disability, (3) required or prolonged a hospitalization, or (4) were judged by the investigator to represent a clinically significant hazard or harm to the participant that might require intervention (medical or surgical) to prevent one of 3 previously mentioned events listed above. HR indicates hazard ratio.

for the majority of CVD outcomes in the present study. Some of these different observations between studies may be secondary to differences in study population or follow-up duration. There was some suggestion in our study that OH may be associated with nonmyocardial infarction ACS. Participants with OH in the setting of intensive therapy had 2.5× the risk of nonmyocardial infarction ACS compared with those without OH, which could support a role for treatment-related OH in the pathogenesis of coronary ischemia. However, these findings are based on a small number of events and should be confirmed. Further, as previously reported,[14,15] intensive treatment significantly reduced the incidence of OH, the incidence of which was 20× more frequent than nonmyocardial infarction ACS in SPRINT.[6]

OH was strongly associated with 2 serious adverse events, hypotension, and bradycardia. Both hypotension events and bradycardia were based on mention of symptomatic low BP or heart rate (without specific cutoffs) in admission history and physicals or discharge summaries of hospitalization records. In a prior analysis, baseline OH was nonsignificantly associated with a higher odds of hypotension events (HR, 1.58 [95% CI, 0.96–2.62]).[7] Since OH is a form of hypotension, the relationship between OH and hypotension events may be expected, although OH was not significantly associated with hypotension events in the intensive group. Bradycardia, on the contrary, is an under-recognized cause of OH.[27,28] Given the importance of stroke volume augmentation in maintaining BP with change in position,[29] it is biologically plausible that bradycardia might cause OH, especially in adults with underlying physical attributes (eg, vascular stiffness) where HR is a compensatory mechanism.[30] It is also possible that bradycardia reflects common upstream factors such as underlying cardiac ischemia or autonomic dysfunction. This is an important topic for future study.

Prior analyses of baseline OH in SPRINT demonstrated that while OH was not associated with syncope, it was associated with falls.[7] Our analysis of post-randomization instances of OH confirmed the null association with syncope but did not show an association between OH and falls. This observation suggests that symptomless OH in the setting of hypertension treatment is not a reliable predictor of falls. Ultimately, our finding conflicts with many observational studies, which have demonstrated that OH is a risk factor for syncope[31–33] and falls.[34–38] The exclusion of adults with a standing SBP <110 mm Hg (which would exclude more severe cases of OH) and use of injurious falls for ascertainment (rather than more sensitive methods like fall calendars) may explain some of these differences with observational studies. It is also possible that differences in BP measurement account for differences across studies, as SPRINT followed a rigorous protocol to monitor BP. Despite these issues, it is important to note there was no difference in the associations between OH and serious adverse

Table 4. Association of Post-Randomization Orthostatic Hypotension as a Time-Varying Covariate With Trial Outcomes and Serious Adverse Events by Blood Pressure Goal Assignment, N=8792.

	Standard Blood Pressure Goal			Intensive Blood Pressure Goal			
Outcomes	Events	HR (95% CI)	*P* Value	Events	HR (95% CI)	*P* Value	*P*-Interaction
Primary outcome	369	0.94 (0.62–1.44)	0.79	280	1.04 (0.63–1.72)	0.87	0.52
Secondary outcomes							
Myocardial infarction	144	1.01 (0.51–1.99)	0.98	102	0.87 (0.33–2.26)	0.78	0.81
Acute coronary syndrome	44	0.35 (0.05–2.73)	0.32	40	2.56 (1.04–6.31)	0.04	0.03
Stroke	85	0.52 (0.18–1.50)	0.23	71	1.18 (0.42–3.32)	0.75	0.35
Heart failure	105	1.33 (0.66–2.69)	0.42	82	0.34 (0.10–1.23)	0.10	0.15
Death from cardiovascular causes	72	0.72 (0.25–2.09)	0.55	50	0.53 (0.12–2.40)	0.41	0.79
Death from any cause	201	1.40 (0.85–2.29)	0.18	163	0.72 (0.35–1.48)	0.37	0.19
Primary outcome or death	475	1.09 (0.76–1.55)	0.65	381	1.01 (0.66–.56)	0.95	0.88
Serious adverse events							
Hypotension	74	3.26 (1.56–6.81)	0.002	146	1.35 (0.71–2.59)	0.36	0.31
Syncope	103	1.57 (0.72–3.43)	0.26	144	1.55 (0.82–2.95)	0.18	0.87
Bradycardia	78	1.96 (0.92–4.18)	0.08	98	1.85 (0.89–3.86)	0.10	0.63
Electrolyte abnormality	125	0.99 (0.46–2.10)	0.97	173	0.91 (0.46–1.80)	0.79	0.92
Injurious fall	305	1.17 (0.74–1.84)	0.50	349	1.14 (0.73–1.78)	0.56	0.72
Acute kidney injury or acute renal failure	118	1.77 (0.88–3.55)	0.11	199	0.99 (0.51–1.93)	0.97	0.19

Models were adjusted for baseline orthostatic hypotension and the following baseline characteristics: age, sex, race, treatment assignment, systolic blood pressure, diastolic blood pressure, body mass index, high-density lipoprotein cholesterol, total cholesterol, statin use, chronic kidney disease, estimated glomerular filtration rate, subclinical or clinical cardiovascular disease, smoking status, or number of hypertensive medications stratified by research site. HR indicates hazard ratio.

events across intensive and standard BP goals, suggesting that OH is not a consequence of more aggressive hypertension treatment that contributes to syncope or falls.

This study has limitations. First, OH was measured using a seated to standing protocol after 1 minute of standing. There is evidence that OH measurements within 1 minute of standing may be more predictive of subsequent falls.[31,38] Also, seated versus supine-to-standing protocols can miss cases of OH as gravitational effects on BP are blunted.[39] Second, our study did not include noninjurious falls. Although inpatient or emergency department claims are specific, a substantial number of fall claims are found only in outpatient records or may never be reported to health professionals.[34] Third, the study excluded people with a standing SBP <110 mm Hg, diabetes mellitus, prior stroke, and dementia, conditions which have been associated with OH in other studies.[15,40,41] As a result, the most severe cases of OH may not be represented in our study. Moreover, about 93% of participants with OH were asymptomatic. As a result, these results may not be generalizable to all OH patients as OH is rarely screened for in asymptomatic patients. Fourth, our results were observed in the context of the treatment regimens used in SPRINT, which are consistent with previous and current US hypertension guidelines. It is possible that more frequent use of other classes of drugs might be associated with more OH and serious adverse events. Finally, given the observational design of our secondary analysis, the nonrandomized contrasts in our study are subject to residual confounding.

Our findings have important clinical implications. SPRINT demonstrated a survival benefit from more aggressive hypertension treatment in both middle aged and older adults at increased risk for CVD.[6,10] It has reshaped how hypertension is defined and established lower goals for therapy.[42] One of the major impacts of SPRINT was that medical treatment of hypertension was recommended by some major guidelines for 82 million adults in the United States, including many healthy adults aged ≥75 years with BP above 130/80 mm Hg.[43] These expanded treatment recommendations have led to the concern, particularly for geriatric populations, that more aggressive hypertension treatment might increase OH, contributing to falls, syncope, and even in some cases CVD events. The present study should allay these concerns. OH was not associated with a higher risk of CVD events, falls, or syncope. Further, there was no evidence that OH in the setting of intensive therapy was more strongly related to the majority of outcomes and adverse events examined. Although further research is needed to examine the association between OH and nonmyocardial infarction ACS, given the primary survival benefits from more aggressive hypertension treatment among older adults, the detection of OH does not represent a clear contraindication for treatment.

Perspectives

In conclusion, in this population of middle-aged and older hypertensive adults, in addition to the previous observation that more aggressive hypertension treatment reduced (rather than increased) the risk of OH,[6] we found that OH was not associated with a higher risk of CVD events, falls, or syncope. Moreover, BP goal did not alter the relationship between OH and risk of CVD events or adverse effects with the exception of nonmyocardial infarction ACS. These findings provide

strong evidence that the presence of symptomless OH should not be a reason for down-titration of medications, even in the setting of a lower BP goal.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Orthostatic hypotension was not associated with higher risk of cardiovascular events, falls, or syncope. Hypertension treatment did not alter the association between orthostatic hypotension and cardiovascular outcomes or adverse events.

What Is Relevant?

- There are ongoing concerns that orthostatic hypotension in the setting of more intensive blood pressure treatment represents a greater risk of adverse events from treatment. Our data challenges this notion and the practice of reducing hypertension treatment in response to orthostatic hypotension.

Summary

Orthostatic hypotension should not be a reason for down-titration of medications, even in the setting of a lower blood pressure goal.