The Association of Orthostatic Hypotension With Ambulatory Blood Pressure Phenotypes in SPRINT

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BACKGROUND
Clinic blood pressure (BP) when measured in the seated position, can miss meaningful BP phenotypes, including low ambulatory BP (white coat effects [WCE]) or high supine BP (nocturnal non-dipping). Orthostatic hypotension (OH) measured using both seated (or supine) and standing BP, could identify phenotypes poorly captured by seated clinic BP alone.

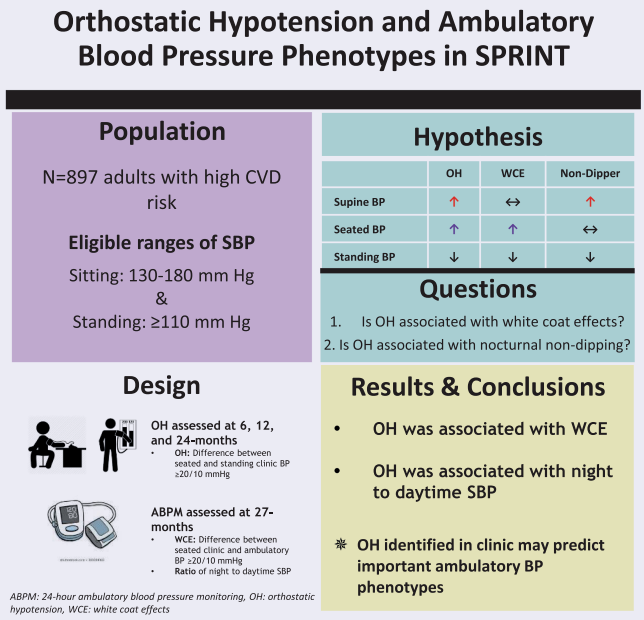
METHODS
We examined the association of OH with WCE and night-to-daytime systolic BP (SBP) in a subpopulation of SPRINT, a randomized trial testing the effects of intensive or standard (<120 vs. <140 mm Hg) SBP treatment strategies in adults at increased risk of cardiovascular disease. OH was assessed during follow-up (6, 12, and 24 months) and defined as a decrease in mean seated SBP ≥20 or diastolic BP ≥10 mm Hg after 1 min of standing. WCE, based on 24-hour ambulatory BP monitoring performed at 27 months, was defined as the difference between 27-month seated clinic and daytime ambulatory BP ≥20/≥10 mm Hg. Reverse dipping was defined as a ratio of night-to-daytime SBP >1.

RESULTS
Of 897 adults (mean age 71.5±9.5 years, 29% female, 28% black), 128 had OH at least once. Among those with OH, 15% had WCE (vs. 7% without OH). Moreover, 25% of those with OH demonstrated a non-dipping pattern (vs. 14% without OH). OH was positively associated with both WCE (OR=2.24; 95%CI: 1.28, 4.27) and reverse dipping (OR=2.29; 95% CI: 1.31, 3.99).

CONCLUSIONS
The identification of OH in clinic was associated with two BP phenotypes often missed with traditional seated BP assessments. Further studies on mechanisms of these relationships are needed.

CLINICAL TRIALS REGISTRATION
Trial Number NCT03569020.

GRAPHICAL ABSTRACT



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Hypertension is endemic in the United States and updated guidelines recommend treating to blood pressure (BP) goals based on seated, clinic-based measurements.[1,2] However, clinic-based BP measurements often did not agree with 24-hour ambulatory BP monitoring (ABPM) measurements in Systolic

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Blood Pressure Intervention Trial (SPRINT).[3] Furthermore, hypotensive events were among the most common complications of intensive BP treatment in SPRINT.[3,4] One limitation of clinic-based BP assessments are that measurements are performed in a single, rested position. This misses important fluctuations in BP that occur in standing or supine positions assumed by patients in home settings throughout the day and night.

Orthostatic hypotension (OH) is a clinic-based measure of BP change that involves measuring BP in at least 2 positions—supine or seated and then standing. OH is defined by a large drop in systolic BP (SBP) ≥20 mm Hg or diastolic BP (DBP) ≥10 mm Hg,[5,6] and is common among older adults[7] with hypertension[8] and in the setting of hypertension treatment.[9] Moreover, we recently demonstrated that OH was an important predictor of hypotension outside of the clinic in SPRINT.[10] Given that OH is a measure of discordant physiology between seated (or supine) and standing (or upright BP), it is possible that it could be used to detect discordance between seated clinic BP measurements and low ambulatory BP (i.e., white coat effects [WCEs]) or high supine BP (i.e., nocturnal nondipping). However, this has never been examined in SPRINT.

The purpose of this study was to compare the association of OH measured during 6-, 12-, and 24-month follow-up visits with the following patterns of 24-hour ABPM at 27 months in SPRINT: (i) WCE, i.e., the ambulatory minus clinic BP and (ii) night-to-daytime BP. We hypothesized that BP differences observed after transitioning from seated to standing positions would be associated with WCE and elevated nocturnal (supine) BP.

METHODS

Study overview

The study design and methods of SPRINT have been previously published.[4,11,12] In brief, SPRINT was a NIH-funded, prospective, randomized, controlled, and open-label outcome trial with blinded end point determination performed at 102 clinical sites in the United States and Puerto Rico from November 2010 to August 2015. SPRINT compared intensive treatment to a SBP goal <120 mm Hg and standard treatment to a SBP goal <140 mm Hg. Institutional Review Boards at each clinical site approved the original study protocol, including subsequent analyses. All SPRINT participants provided written informed consent. A subset of the SPRINT population at 15 sites also consented to an IRB-approved, 24-hour ABPM ancillary study performed at the 27-month follow-up visit.[13]

Study participants

SPRINT recruited 9,361 participants, who were at least 50 years old with clinic SBP of 130–180 mm Hg, depending on number of antihypertensive medications they were taking during the screening visit. Participants had at least 1 cardiovascular disease (CVD) risk factor: presence of clinical or subclinical CVD other than stroke, an estimated glomerular filtration rate (based on the Modification of Diet in Renal Disease study equation) of 20–59 ml/min/1.73 m^2, Framingham 10-year risk score ≥15%, or age ≥75 years. Exclusion criteria included diabetes mellitus, previous stroke, symptomatic heart failure in the past 6 months, advanced chronic kidney disease (estimated glomerular filtration rate <20 ml/min/1.73 m^2), left ventricular ejection fraction <35%, any organ transplant, dialysis, proteinuria >1 g/day, dementia, and SBP <110 mm Hg after 1 minute of standing at a screening visit.

Our study population was restricted to participants who completed the ABPM ancillary study. This ancillary excluded participants for the following reasons: their arm circumference was >50 cm, they were a shift worker or worked regularly at night, they had a history of breast cancer requiring mastectomy or radiation on the nondominant arm and needed to avoid frequent BP measurements due to lymphedema, or they had end-stage renal disease. Ultimately, of the 1,003 participants who consented to ABPM measurements, 925 participants were eligible and underwent ABPM, and 897 had complete ABPM data as defined below.

Office BP measurement

Seated office BP was measured 3 times at 1-minute intervals after a 5-minute rest period, using a validated automated oscillometric measurement device (HEM-907XL, Omron Healthcare, Lake Forest, IL) and standardized procedures.[11,14,15]

Orthostatic hypotension

OH was assessed at screening, baseline, 1-, 6-, and 12-month visits, and then annually thereafter. Participants were instructed to stand after seated office BP measurement, and after 1 minute of standing, BP was measured again.[10,16,17] OH was defined using the consensus definition of a decrease in SBP ≥20 mm Hg or DBP ≥10 mm Hg from the seated to standing positions.[5,6] For our main analysis, we assessed for presence of OH at 6, 12, or 24 months. OH presence was defined as: never, isolated (1 occurrence), or recurrent (2 or 3 occurrences). OH was also defined as a dichotomous outcome (present at any of 6-, 12-, or 24-month visits). Given that ABPM was performed in the setting of SPRINT's treatment protocol, we excluded the screening and baseline OH assessments to avoid introducing pretreatment effects on OH occurrence.[18] We also excluded the 1-month visit as BP treatment was actively titrated during this time[4] and excluded OH assessments after ABPM was performed. We also performed a sensitivity analysis defining OH based on the 24-month visit alone. This approach was not used in our primary analysis as OH is a recurrent event and there were fewer adults with OH at the 24-month visit.

Ambulatory BP

ABPM was conducted over 24 hours within 3 weeks of the 27-month study visit using a validated device, SpaceLabs 90207 (Snoqualmie, WA).[19] The monitor was placed on the participants' nondominant arm and configured to measure

BP every 30 minutes. An ABPM recording period was deemed to be complete if there were ≥14 readings between 6:00 AM and 12:00 AM and ≥6 readings between 12:00 AM and 6:00 AM.[13,20,21] Daytime SBP and daytime DBP were defined as the mean of all SBP readings and DBP readings, respectively, during the 9:00 AM to 9:00 PM window; nighttime SBP and nighttime DBP were defined as the average of all SBP readings and DBP readings, respectively, during the 1:00 AM to 6:00 AM window.[22] Twenty-four hour SBP and daytime DBP were defined as the mean of all SBP readings and DBP readings, respectively, over the entire monitoring period.

Our primary outcomes were: (i) WCE defined as a difference between clinic and daytime SBP ≥20 mm Hg or daytime DBP ≥10 mm Hg and (ii) nocturnal dipping status defined as the ratio of night-to-daytime SBP, which was further classified as extreme dipping <0.8, normal dipping 0.8 to <0.9, nondipping 0.9 to 1, and reverse dipping >1.[23] Note that WCE based on SBP is presented in the main text, while WCE based on DBP is presented in Supplementary Material online. We also examined white coat hypertension defined as clinic BP ≥140/90 mm Hg and daytime ambulatory BP <135/85 mm Hg.[24] Other BP phenotypes of interest derived from ABPM were: (i) masked hypertension (clinic BP <140/90 mm Hg and daytime ambulatory BP ≥135/85 mm Hg), (ii) controlled hypertension (clinic BP <140/90 mm Hg and daytime ambulatory BP <135/85 mm Hg), and (iii) sustained hypertension (clinic BP ≥140/90 mm Hg and daytime ambulatory BP ≥135/85 mm Hg).

Covariates

In general, we used covariate information assessed in closest proximity to the 27-month ABPM measurement (i.e., the 24-month visit). However, some data were only assessed at baseline, which was used if 24-month data was not available. Age, sex, race/ethnicity (black, white, other, Hispanic), and baseline smoking status (never, current, former) were self-reported at baseline. Body mass index was determined using height and weight measurements at the 24-month visit. Chronic kidney disease was based on measured creatinine at baseline and the 24-month visit and defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2, using the 4 variable Modification of Diet in Renal Disease equation. High-density lipoprotein cholesterol and total cholesterol were measured in serum using standard assays during the 24-month visit. History of CVD was based on self-reported CVD at baseline or incident cases between baseline and the 24-month visit. Diabetes was based on self-report at the 24-month visit. Prior stroke was determined based on adjudicated events up through the 24-month visit.[3,4,10,11,13]

Statistical analysis

We compared baseline characteristics between participants with and without OH, using means and proportions. We used logistic regression for WCE as a dichotomous variable and linear regression for WCE as a continuous variable to examine the association with OH, postural change in BP, and orthostatic hypertension. Models were adjusted for age, sex, and race/ethnicity (model 1). We additionally adjusted for smoking status, chronic kidney disease (at baseline and at 24 months), body mass index, high-density lipoprotein cholesterol, total cholesterol, CVD, and treatment group (model 2). A test for interaction was performed to examine effect modification by treatment group. Given the absence of a statistical interaction between exposures and treatment group, all analyses are primarily presented using the pooled study population, combining intensive and standard BP treatment groups, while results by treatment assignment are presented in Supplementary Material online.

Models were repeated for night-to-daytime SBP and DBP ratio, using linear regression. We also used multinomial logistic regression to study the association between OH BP measures and dipping categories (dippers, extreme dippers, nondippers, and reverse dippers) with dippers serving as the reference group.

In sensitivity analyses, we defined OH, postural change in BP, and orthostatic hypertension using the 24-month visit assessment alone. We also characterized mean seated, standing and ambulatory SBP and DBP by OH, WCE, and nondipping status. Analyses were conducted using the R Statistical Computing Environment. *P* values were 2 sided and not adjusted for multiple comparisons.

RESULTS

Overall, the mean age of the 897 SPRINT participants in our analyses at the 27-month follow-up visit was 71.5 ± 9.5 years; 28.7% were female, and 28.0% were black (Table 1). The mean 27-month clinic SBP was 127.6 ± 15.6 mm Hg and the mean 27-month clinic DBP was 69.7 ± 12.0 mm Hg; 128 participants (14.3%) had OH during follow-up visits prior to the 27-month visit (Table 2). Among those assigned to intensive treatment, 12.6% had OH during follow-up visits prior to the 27-month visit, while 16.0% had OH among those assigned to standard treatment. Notably there was no evidence of a difference between treatment groups for the incidence of OH prior to the 27-month study visit; thus both treatment groups were combined in ensuing analyses.

The following OH BP measurements were significantly associated with a higher odds of WCE: any OH (odds ratio [OR] 2.34; 95% confidence interval [CI]: 1.28, 4.27), isolated OH (OR 2.36; 95% CI: 1.22, 4.55), and postural change per 1 mm Hg (OR 1.06; 95% CI: 1.02, 1.11) (Table 3, Supplementary Tables ST1 and ST2 online). In contrast, change in DBP and orthostatic hypertension was not associated with WCE. Sensitivity analyses with WCE modeled as a continuous variable based on SBP were confirmatory, in that any OH, isolated OH, and postural change in SBP were all associated with WCE (Supplementary Table ST3 online). In contrast, sensitivity analyses with WCE as a continuous variable based on DBP were generally attenuated (Supplementary Table ST4 online). Furthermore,

Table 1. Characteristics of SPRINT (Systolic Blood Pressure Intervention Trial) participants in the ambulatory blood pressure ancillary study by orthostatic hypotension history at the 6-, 12-, or 24-month SPRINT study visit, mean (SD) or %

Variable	Total *N* = 897	Orthostatic hypotension at least once during 6-, 12-, and 24-month visits *N* = 128	No occurrence of orthostatic hypotension *N* = 769
Intensive treatment group, %	50.5	44.5	51.5
Standard treatment group, %	49.5	55.4	48.5
Age, years (27-mo)	71.5 (9.5)	72.8 (9.9)	71.3 (9.4)
Female, %	28.7	25.0	29.3
Race/ethnicity, %			
Black	28.0	23.4	28.7
White	67.3	70.3	66.8
Other	2.3	4.7	2.0
Hispanic	2.3	1.6	2.5
Body mass index, kg/m^2 (24-mo)	29.5 (5.6)	27.9 (5.0)	29.8 (5.7)
Smoking, %			
Never	46.2	39.1	47.4
Former	43.6	46.1	43.2
Current	10.2	14.8	9.4
History of CKD (baseline), %	29.2	30.2	29.1
History of CVD (baseline), %	21.7	25.8	21.1
Experienced CVD event before ABPM[a], %	3.2	3.1	3.3
Diabetes (24-mo), %	2.3	2.3	2.3
Stroke (24-mo), %	0.1	0.0	0.1
CKD (24-mo), %	32.4	33.6	32.2
HDL, mg/dl (24-mo)	53.1 (17.0)	56.2 (18.2)	52.6 (16.7)
Total cholesterol, mg/dl (24-mo)	181.0 (39.4)	180.3 (40.5)	181.1 (39.2)

24-mo, data collected at 24-month annual visit; 27-mo, data collected at 27-month study visit. Abbreviations: ABPM, ambulatory BP monitoring; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate based on the Modification of Diet in Renal Disease study equation; HDL, high-density lipoprotein.

[a]After randomization.

in a sensitivity analysis examining white coat hypertension, OH, and postural change in SBP were associated with white coat hypertension (Supplementary Table ST5 online).

Any OH was positively associated with a higher night-to-daytime SBP ratio (β = 0.04; 95% CI: 0.02, 0.06) (Table 4, Supplementary Tables ST6 and ST7 online). Moreover, isolated and recurrent OH were also associated with a higher night-to-daytime SBP ratio (β = 0.03; 95% CI: 0.01, 0.05 and β = 0.08; 95% CI: 0.05, 0.12, respectively). Every 1 mm Hg postural reduction in SBP or DBP was associated with higher night-to-daytime SBP ratio (β = 0.003; 95% CI: 0.001, 0.004 and β = 0.004; 95% CI: 0.002, 0.006, respectively). Recurrent orthostatic hypertension was inversely associated with night-to-daytime SBP ratio (β = −0.04; 95% CI: −0.05, −0.02). Analyses were repeated with night-to-daytime DBP ratio and were similar with any OH, recurrent OH, and postural change in SBP or DBP being associated with high night-to-day DBP ratio (Supplementary Table ST8 online). Similarly, recurrent orthostatic hypertension was inversely associated with night-to-day DBP ratio.

Reverse dippers were associated with OH (OR 2.27; 95% CI: 1.30, 3.97), recurrent OH (OR 7.68; 95% CI 2.32, 25.5), postural change in SBP (OR 1.08; 95% CI: 1.04, 1.12), and postural change in DBP (OR 1.13; 95% CI: 1.05, 1.21) (Table 5, Supplementary Tables ST9 and ST10 online). Orthostatic hypertension was not associated with nocturnal dipping categories after adjustment (Supplementary Tables ST11 and ST12 online).

Sensitivity analyses with OH restricted to the 24-month SPRINT study visit were consistent, but attenuated due to the small number with OH (*N* = 70) (Supplementary Tables ST13–ST16 online).

Characterization of seated and standing BP by OH, WCE, and dipping status showed that seated SBP and DBP were substantially greater among those with WCE vs. those with

Table 2. Blood pressure characteristics of SPRINT (Systolic Blood Pressure Intervention Trial) participants in the ambulatory blood pressure ancillary study by orthostatic hypotension history at the 6-, 12-, or 24-month SPRINT study visit, mean (SD) or %

Variable	Total *N* = 897	Orthostatic hypotension at least once during 6-, 12-, and 24-month visits *N* = 128	No occurrence of orthostatic hypotension *N* = 769
Clinic SBP, mm Hg (27-mo)	127.6 (15.6)	129.2 (17.1)	127.4 (15.3)
Clinic DBP, mm Hg (27-mo)	69.7 (12.0)	69.7 (13.1)	69.7 (11.8)
White coat effect, %	8.3	14.8	7.2
Dipping status, %			
Extreme dipper	10.3	3.1	11.4
Dipper	35.3	28.1	36.5
Nondipper	38.8	43.8	38.0
Reverse dipper	15.6	25.0	14.0
BP phenotypes, %			
White coat hypertension	5.7	10.2	4.9
Masked hypertension	26.2	25.0	26.4
Controlled hypertension	51.1	48.4	51.6
Sustained hypertension	17.0	16.4	17.1
N antihypertensive medications (27-mo)	2.3 (1.3)	2.4 (1.3)	2.3 (1.3)

24-mo, data collected at 24-month annual visit; 27-mo, data collected at 27-month study visit. Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; *N* antihypertensive medication, number of antihypertensive medications; SBP, systolic blood pressure. Participant BP phenotypes were defined as follows: (i) white-coat hypertension (clinic BP ≥140/90 mm Hg and daytime ambulatory BP <135/85 mm Hg), (ii) masked hypertension (clinic BP <140/90 mm Hg and daytime ambulatory BP ≥135/85 mm Hg), (iii) controlled hypertension (clinic BP <140/90 mm Hg and daytime ambulatory BP <135/85 mm Hg), and (iv) sustained hypertension (clinic BP ≥140/90 mm Hg and daytime ambulatory BP ≥135/85 mm Hg).

nondipping status, regardless of OH (Supplementary Table ST17 online).

DISCUSSION

In this study of hypertensive, middle-aged and older adults, OH was associated with low BP outside of clinic (WCE) and high supine BP (reverse nocturnal dipping). These findings suggest a potential role of OH in identifying 2 BP phenotypes related to complications of BP treatment and CVD events.[23,25]

WCEs are prevalent in older adults,[26,27] and represent an important challenge to BP treatment. In fact, hypotension events outside of the clinic setting were among the most common complications of intensive treatment in SPRINT, and OH was a strong predictor of hypotension events.[4,10] While WCEs have been attributed to a number of factors, including the clinic environment, BP measurement technique, or even physiologic responses,[28,29] it is also possible that BP measurement in the seated position simply misses BP excursions associated with standing that are captured with an ambulatory protocol. It is also biologically plausible that both OH and WCE are related via shared autonomic dysfunction.[30] Further research is needed to elucidate mechanisms of the relationship between OH and WCE.

OH is a dynamic clinical BP assessment long associated with autonomic regulation.[5] However, emerging evidence has shown that OH is a strong predictor of CVD events.[7,31–35] Mechanisms of this association have often focused on poor heart rate augmentation or endothelial stiffness underlying BP drops after standing.[36] Our study highlights sleep-time elevations in BP as another mechanism by which OH may be related to CVD events. BP fluctuates over a 24-hour period with a general trend toward lower BPs during sleep.[37] This reduction in sleep-time BP is associated with a lower risk of CVD events, while nondipping or reverse dipping have been associated with a higher risk of CVD events.[23] Some have even considered the absence of diurnal variation in BP to explain the higher risk of CVD among evening shift workers.[38] However, nondipping or even reverse dipping patterns cannot be diagnosed without ABPM, causing these conditions to go undetected in many patients. Our study demonstrates that OH was strongly associated with day-to-nighttime sleep ratio and reverse dipping status. Thus, OH may represent a useful clinic-based tool for identifying elevated BP at night.

Our study has limitations. OH and ABPM were not measured concurrently, which may have attenuated the association between OH BP measures and ABPM. As a result, the observed associations between OH and BP phenotypes may be even stronger than suggested by our report. Furthermore, ABPM was performed in the setting of BP treatment and thus some BP phenotypes (e.g., white coat hypertension) were rare due to treatment protocols in the trial. In addition, OH was not very common, which may be due to SPRINT's seated (vs. supine) BP measurements that were

Table 3. Association of orthostatic hypotension, postural change in SBP and DBP, and orthostatic hypertension (at 6, 12, or 24 months) with white coat effect as a dichotomous outcome variable defined as the difference between clinic and ABPM daytime SBP ≥20 mm Hg or DBP ≥10 mm Hg

Odds ratio [95% CI]	Crude	Model 1	Model 2
Orthostatic hypotension (6, 12, and 24 months; *N* = 128)	2.26 [1.29, 3.95]	2.30 [1.31, 4.05]	2.33 [1.28, 4.25]
Orthostatic hypotension			
Never (*N* = 769)	Reference	Reference	Reference
Isolated (*N* = 100)	2.11 [1.13, 3.96]	2.16 [1.15, 4.07]	2.35 [1.22, 4.53]
Recurrent (*N* = 28)	2.82 [1.03, 7.70]	2.84 [1.03, 7.83]	2.27 [0.72, 7.11]
Postural change in SBP[a] (for every −1 mm Hg)	1.06 [1.02, 1.11]	1.06 [1.01, 1.10]	1.10 [1.04, 1.17]
Postural change in DBP[a] (for every −1 mm Hg)	1.05 [0.97, 1.13]	1.05 [0.98, 1.13]	1.05 [0.97, 1.13]
Orthostatic hypertension (6, 12, and 24 months; *N* = 348)	1.02 [0.62, 1.65]	0.99 [0.61, 1.63]	0.97 [0.57, 1.64]
Orthostatic hypertension			
Never (*N* = 549)	Reference	Reference	Reference
Isolated (*N* = 225)	1.09 [0.63, 1.89]	1.09 [0.62, 1.89]	1.08 [0.59, 1.94]
Recurrent (*N* = 123)	0.88 [0.42, 1.86]	0.84 [0.40, 1.78]	0.79 [0.35, 1.79]

Model 1: age, sex, race/ethnicity. Model 2: smoking status (baseline), chronic kidney disease (baseline), chronic kidney disease (24 months), BMI (baseline), HDL (24 months), total cholesterol (24 months), cardiovascular disease (between baseline and 24 months), treatment group. Abbreviations: ABPM, ambulatory BP monitoring; BMI, body mass index; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

[a]Postural change = average of the difference of standing − seated BP at 6, 12, and 24 months.

Table 4. Association of orthostatic hypotension, postural change in SBP and DBP, and orthostatic hypertension (at 6, 12, or 24 months) with ratio of night-to-daytime SBP

Beta coefficient [95% CI]	Crude	Model 1	Model 2
Orthostatic hypotension (6, 12, and 24 months; *N* = 128)	0.04 [0.02, 0.06]	0.04 [0.02, 0.06]	0.04 [0.02, 0.06]
Orthostatic hypotension			
Never (*N* = 769)	Reference	Reference	Reference
Isolated (*N* = 100)	0.03 [0.01, 0.05]	0.03 [0.01, 0.05]	0.03 [0.01, 0.05]
Recurrent (*N* = 28)	0.08 [0.05, 0.12]	0.08 [0.05, 0.12]	0.08 [0.05, 0.12]
Postural change in SBP[a] (for every −1 mm Hg)	0.003 [0.002, 0.004]	0.003 [0.001, 0.004]	0.003 [0.001, 0.004]
Postural change in DBP[a] (for every −1 mm Hg)	0.003 [0.002, 0.005]	0.004 [0.002, 0.005]	0.004 [0.002, 0.006]
Orthostatic hypertension (6, 12, and 24 months; *N* = 348)	−0.008 [−0.02, 0.008]	−0.013 [−0.03, 0.003]	−0.0013 [−0.03, 0.003]
Orthostatic hypertension (6, 12, and 24 months)			
Never (*N* = 549)	Reference	Reference	Reference
Isolated (*N* = 225)	−0.006 [−0.02, 0.008]	−0.007 [−0.02, 0.007]	−0.005 [−0.01, 0.009]
Recurrent (*N* = 123)	−0.03 [−0.05, −0.01]	−0.03 [−0.05, −0.02]	−0.04 [−0.05, −0.02]

Model 1: age, sex, and race/ethnicity. Model 2: smoking status (baseline), chronic kidney disease (baseline), chronic kidney disease (24 months), BMI (baseline), HDL (24 months), total cholesterol (24 months), cardiovascular disease (between baseline and 24 months), and treatment group. Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

[a]Postural change = average of the difference of standing − seated BP at 6, 12 and 24 months.

delayed beyond 1 minute. We have shown that earlier OH assessments and symptoms may be more strongly associated with adverse clinical events.[39,40] Moreover, by 27 months SPRINT participants were familiar with the study staff and protocol, which may underestimate the prevalence of WCEs. Another limitation is that we did not have ecologic data on the participant's position at the time of each ABPM measurements. Finally, our study was observational and thus is subject to residual confounding.

Our study also has strengths. SPRINT represents one of the largest studies of both OH and ABPM in adults with hypertension. There are few studies with both OH and ABPM assessments, mostly in populations with established dementia (largest $N = 200$).[41–46] Further, BP

Table 5. Association of orthostatic hypotension, categories of orthostatic hypotension (at 6, 12, or 24 months), and postural change in BP with nocturnal dipping categories

	Crude (Ref: dipper, *n* = 317)			Model 1 (Ref: dipper, *n* = 317)			Model 2 (Ref: dipper, *n* = 317)		
OR [95% CI]	Extreme dippers (*n* = 92)	Nondipper (*n* = 348)	Reverse dippers (*n* = 140)	Extreme dippers (*n* = 92)	Nondipper (*n* = 348)	Reverse dippers (*n* = 140)	Extreme dippers (*n* = 92)	Nondipper (*n* = 348)	Reverse dippers (*n* = 140)
Orthostatic hypotension (6, 12, and 24 months; *N* = 128)	0.31 [0.12, 1.02]	1.04 [0.95, 2.35]	2.31 [1.37, 3.91]	0.36 [0.12, 1.03]	1.54 [0.97, 2.43]	2.42 [1.42, 4.15]	0.29 [0.01, 0.86]	1.38 [0.86, 2.21]	2.29 [1.31, 3.99]
Orthostatic hypotension									
Never (*N* = 769)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Isolated (*N* = 225)	0.39 [0.14, 1.16	1.32 [0.82, 2.14]	1.62 [0.89, 2.96]	0.41 [0.14, 1.19]	1.38 [0.84, 2.25]	1.71 [0.93, 3.15]	0.35 [0.12, 1.03]	1.22 [0.74, 2.02]	1.64 [0.87, 3.08]
Recurrent (*N* = 123)	0.002 [3×10^{-23}, 7×10^{16}]	2.89 [0.92, 9.07]	7.81 [2.47, 24.8]	4×10^{-6} [4×10^{-6}, 4×10^{-6}]	2.83 [0.89, 8.96]	8.11 [2.51, 26.12]	10^{-6} [10^{-6}, 10^{-6}]	2.65 [0.82, 8.51]	7.70 [2.32, 25.6]
Postural Change in SBP[a] (for every −1 mm Hg)	0.97 [0.93, 1.02]	1.03 [1.00, 1.06]	1.08 [1.04, 1.12]	0.98 [0.93, 1.02]	1.03 [0.99, 1.06]	1.08 [1.04, 1.12]	0.96 [0.92, 1.01]	1.03 [1.00, 1.06]	1.08 [1.04, 1.12]
Postural Change in DBP[a] (for every −1 mm Hg)	0.98 [0.91, 1.05]	1.03 [0.99, 1.09]	1.12 [1.05, 1.19]	0.98 [0.931 1.05]	1.04 [0.99, 1.09]	1.13 [1.05, 1.21]	0.96 [0.89, 1.04]	1.05 [1.00, 1.04]	1.13 [1.05, 1.21]

Note: Dipping categories were defined as extreme dipper <0.8, normal dipper 0.8 to <0.9, nondipper 0.9–1, and reverse dipper >1. Model 1: age, sex, race/ethnicity. Model 2: smoking status (baseline), chronic kidney disease (baseline), chronic kidney disease (24 months), BMI (baseline), HDL (24 months), total cholesterol (24 months), cardiovascular disease (between baseline and 24 months), and treatment group. Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; OR, odds ratio; SBP, systolic blood pressure.

was assessed in a standardized, rigorous fashion in clinic, minimizing imprecision. Finally, OH was measured multiple times, allowing us to examine recurrent and isolated OH phenotypes.

Our study has clinical implications. While 24-hour ABPM continues to be viewed as the gold standard BP assessment,[2,47] it remains inaccessible to many patients due to costs and logistics, often requiring 2 in-person visits. This is particularly problematic for adults in rural communities or lacking healthcare access. Our study demonstrates how a BP assessed in 2 positions in clinic can help identify 2 important ABPM phenotypes. However, these findings require replication and assume that clinic BP is measured according to guidelines,[48] while in routine practice the quality of BP measurements varies greatly.[49,50] Adding standing BP to routine clinic visits might be challenging in the clinical setting (time, training), but should be the focus of subsequent studies to determine whether OH assessments might improve BP treatment.

In conclusion, in this population of middle-aged and older hypertensive adults, OH was associated with WCE and elevated sleep-time BP. OH may represent a practical, clinic-based approach for detecting BP phenotypes outside of the clinic when ABPM is not available, but these findings require replication.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

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DISCLOSURE

The authors declared no conflict of interest.

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