Effect of Postural Hypotension on Recurrent Stroke: Secondary Prevention of Small Subcortical Strokes (SPS3) Study

Tapan Mehta, MD, MPH,* Leslie A. McClure, PhD, MS,† Carole L. White, PhD, RN,‡ Addison Taylor, MD, PhD,§ Oscar R. Benavente, MD, FRCPC,‖ and Kamakshi Lakshminarayan, MBBS, PhD, MS#

Background: Orthostatic hypotension (OH) has been independently associated with increased risk of stroke and other cardiovascular events. We sought to investigate the relationship between OH at follow-up and recurrent stroke risk in SPS3 (Secondary Prevention of Small Subcortical Strokes) trial patient cohort. This is a retrospective cohort analysis. *Methods:* We included all SPS3 trial participants with blood pressure measurements in both sitting and standing position per protocol at baseline, with at least 1 follow-up visit to establish the relationship between OH at follow-up and recurrent stroke risk (primary outcome). Secondary outcomes included major vascular events, myocardial infarction, all-cause mortality, and, ischemic and hemorrhagic stroke subtypes. Participants were classified as having OH at baseline and at each follow-up visit based on a systolic BP decline ≥20 mm Hg or a diastolic BP decline ≥10 mm Hg on position change from sitting to standing. We used Cox proportional hazards regression modeling to compare the risk of outcomes among those with and without OH. *Results:* A total of 2275 patients were included with a mean follow up time 3.2 years (standard deviation = 1.6 years). 39% (881/2275) had OH at some point during their follow-up. Of these, 41% (366/881) had orthostatic symptoms accompanying the BP drop. In a fully adjusted model, those with OH had a 1.8 times higher risk of recurrent stroke than those without OH (95% confidence interval: 1.1-3.0). The risk of ischemic stroke, major vascular events, and all-cause mortality was similarly elevated among the OH group. *Conclusion:* OH was associated with increased recurrent stroke risk, vascular events, and all-cause death in this large cohort of lacunar stroke patients. Whether minimizing OH in the management of poststroke hypertension in patients with lacunar stroke reduces recurrent stroke risk deserves further study.

Key Words: Recurrent stroke—orthostatic hypotension—hypertension—small sub-cortical strokes

Introduction

The treatment of hypertension (HTN) is possibly the most important intervention for the secondary prevention of ischemic stroke.[1] One common side effect of antihypertensive medications is orthostatic hypotension (OH) or a substantial fall in blood pressure (BP) upon standing. This fall may be accompanied by symptoms or may be asymptomatic. Studies have reported that OH is

From the *Department of Neurology, University of Minnesota, Minneapolis, Minnesota; †Dornsife School of Public Health, Drexel University, Philadelphia, Pennsylvania; ‡School of Nursing, UT Health San Antonio, Texas; §Michael E. DeBakey VA Medical Center & Department of Medicine, Baylor College of Medicine, Houston, Texas; ‖Department of Medicine, Division of Neurology University of British Columbia, Vancouver, British Columbia, Canada; and #Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota.

Received November 7, 2018; revision received March 27, 2019; accepted April 5, 2019.

Address correspondence to Kamakshi Lakshminarayan, MBBS, PhD, MS, Division of Epidemiology and Community Health, University of Minnesota, 1300 S 2nd Street, Suite 300, Minneapolis, MN 55454-1015. E-mails: laksh004@umn.edu, kamakshi@umn.edu.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.04.009

associated with an increased risk of ischemic stroke in the general population[2] and also that orthostatic variation (both increase and decrease in BP on standing) was associated with an increased risk of incident lacunar infarcts.[3,4] Most studies on OH and stroke have reported on incident stroke events. Less is known about the association between OH and recurrent stroke. Since many stroke patients are on antihypertensive medications, it is useful and clinically relevant to understand if there is an association between OH and recurrent strokes and vascular events. This could have implications for choice of antihypertensive medications in stroke survivors with HTN since some antihypertensive medications are more likely to be associated with OH than others.[5,6]

The Secondary Prevention of Small Subcortical Strokes (SPS3) study provides a unique opportunity to examine the relationship between OH and stroke recurrence. The SPS3 study examined the impact of 2 targets of SBP management on stroke recurrence in more than 3000 lacunar stroke survivors.[7] In this manuscript, we examine the relationship between OH and risk of recurrent stroke in the SPS3 cohort. This cohort is very well-suited to answer this question since OH was measured at baseline and follow-up visits using a consistent, standard approach.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the SPS3 publication committee at whitec2@uthscsa.edu.

The SPS3 trial was a randomized, multi-center clinical trial conducted in 81 clinical centers in North America, Latin America, and Spain. Study design details are described elsewhere[8] and summarized here. Patients with recent (within 6 months) symptomatic lacunar infarcts proven by MRI were randomly assigned in a two-by-two factorial design to 2 target levels of systolic BP (1:1; 130-149 mm Hg versus <130 mm Hg; open-label, PROBE design) and to a once-daily antiplatelet treatment (1:1; aspirin 325 mg plus clopidogrel 75 mg versus aspirin 325 mg plus placebo; double-blind). Patients with critical stenosis in cervical or intracranial vessels pertinent to the index event as well as those with stroke due to other etiologies such cardioembolism from atrial fibrillation were excluded in the SPS3 trial. The primary SPS3 outcome was recurrent stroke. Secondary outcomes were acute myocardial infarction (MI) and death which was classified as due to vascular, nonvascular, or unknown cause.

The SPS3 study took place between March 23, 2003 and April 30, 2012 and a total of 3020 patients were enrolled in the study. Detailed medical history and demographic information was collected at baseline. Study participants were seen monthly for the first 3 months after randomization and until the target BP was achieved at 2 consecutive visits. Thereafter, they were seen quarterly. At each follow-up visit, BP was measured using a standard protocol (Appendix).[8-12] At each visit seated BP (3 readings) as well as standing BP was measured, and a standard questionnaire assessed adverse events including orthostatic symptoms and study outcomes (Appendix). The protocol used for BP measurement and questionnaires for assessment of orthostatic symptoms and other adverse events are included in the Appendix. BP measurements were done by SPS3 affiliated personnel with special training. These measurements were carried out with the Colin electronic sphygmomanometer. In the event of readings which were unexpectedly high or low, a recheck with a recently calibrated mercury manometer was part of the protocol. Orthostatic (standing) measurements obtained after sitting BPs are measured.

The SPS3 study was approved by the institutional review boards of all participating centers, and all patients provided written informed consent. Deidentified data from the study was further analyzed by authors approved for data use.

Study Design and Outcomes

This is a retrospective, cohort study using the cohort of SPS3 trial participants. The primary outcome of interest is recurrent stroke. We also examined secondary outcomes, namely, ischemic and hemorrhagic strokes, MI, vascular events (MI, stroke, cardiovascular death), and all-cause mortality. Definitions of outcome events are available in the online supplement of the primary study manuscript.[13] Our exposure of interest was OH at a follow-up visit. The reason we used OH at a follow-up visit, (rather than baseline OH) was that the baseline BP was sometimes measured soon after stroke, typically, within 3-4 weeks poststroke. BP are often times elevated in the immediate aftermath after stroke due to cerebral dysregulation.[14]

We included all SPS3 participants who had BP measured both sitting and standing by protocol at baseline and also at least 1 follow-up visit. Participants were classified as having OH at baseline and at each follow-up visit based on either (1) a decline in SBP of at least 20 mm Hg, or (2) a decline in DBP of at least 10 mm Hg with posture change from sitting to standing.

We further examined the sensitivity of our results using a more liberal definition of OH which included one of the BP criteria above or the presence orthostatic symptoms on posture change from sitting to standing. These symptoms included 1 or more of the following symptoms upon standing: orthostatic dizziness, lightheadedness, unsteadiness, blurry vision, and, palpitations.

Analysis

We compared baseline characteristics between those with OH at 1 or more follow-up versus those with no OH during follow up using the *t* test or the chi-square test of

association, as appropriate. Cox proportional hazards models were used to compare the risk of events (any stroke, ischemic stroke, hemorrhagic stroke, major vascular events, MI, and death) between those with OH and those without. We included OH as a time-varying covariate in order to account for the strong relationship between OH and the number of follow-ups. Models were fit (1) univariately, (2) with the addition of age, sex, race, and region of the study, (3) with the further addition of smoking, alcohol use, baseline SBP and baseline OH, and (4) with the addition of diabetes, HTN at baseline, the number of antihypertensive medications at baseline, angina, hyperlipidemia, and the BP target group (ie intense versus less intense control). We adjusted for baseline OH in model 3 in order to understand whether the baseline OH had an effect on the relationship between the exposure variable and recurrent stroke risk. Model 4 tested the interaction between OH and diabetes. We also examined the interaction between OH and target BP group of the trial in Model 4. All analyses assessed the definition of OH using BP criteria alone, as well as with the definition of OH using BP criteria and symptom criteria. Finally we computed the E-value for the primary outcome to assess for the extent of unmeasured confounding.[15]

Results

The SPS3 enrolled a total of 3020 participants. Of these, 660 participants were enrolled before the study required the collection of standing BP and an additional 85 participants did not have orthostatic BP collected at any follow-up visit. After, these participants were excluded, a total of 2275 participants were included in this analysis. Mean participant follow-up time was 3.2 years (SD = 1.6 years).

Primary Analysis

Of the 2275 participants, 39% (881/2275) had OH at some point during their follow-up. Of these, 41% (366/881) had orthostatic symptoms accompanying the BP drop. An additional 357 patients reported orthostatic symptoms without meeting the BP criteria and are not classified as having OH in the primary analysis.

Table 1 presents the baseline characteristics of participants overall and by "ever vs. never" OH during follow-up visits. Orthostatic participants were more often women: 41% women in the OH group versus 33% in the non-OH group, (P = .0002). They were more likely to be of the white race 54% white in the OH group versus 46% in the non-OH group, (P = .0002). They were also more likely to be from the US (Table 1). Participants in the OH group had a higher baseline prevalence of hyperlipidemia and a history of angina. Those who were orthostatic at follow-up were more likely to have had OH at baseline and were also in the higher target BP group (ie less intense management with BP goal of 130-149 mm Hg). Participants who were orthostatic at 1 or more follow-up visits had significantly more follow-up visits.

The unadjusted event rates are significantly higher in the non-OH group (Table 2). The incremental models (Table 3) found that OH was significantly associated with all outcome events with the exception of hemorrhagic stroke and MI, even after multivariable adjustment. In a fully adjusted model, those with OH had a 1.8 times higher risk of recurrent stroke than those without OH (95% confidence interval [CI]: 1.1-3.0). The risk of ischemic stroke, major vascular events, and all-cause mortality was similarly elevated among the OH group. There was no significant difference in the relationship between OH and outcomes in diabetics versus non-diabetics (Table 4). Similarly, the interaction between OH and target BP group of the trial in fully adjusted models was nonsignificant (Table 5).

Unmeasured Confounding

The E-value for the hazard ratio for primary outcome (all stroke) and its 95% CI was: 3.1 (1.4, 5.5). This suggests that the observed hazard ratio of 1.8 could be attenuated by an unmeasured confounder that was associated with both the orthostatic HTN and stroke by a relative risk of 3.1 each, beyond the confounders included in our model.

Sensitivity Analysis

When the OH definition was expanded to include either the BP criteria or the presence of orthostatic symptoms, 54% (1238/2275) were defined as having OH at some point during their follow-up. Multivariable model results were similar to the more specific OH definition, although with the exception of all-cause mortality, the hazard ratios were no longer statistically significant between the 2 groups (online Tables 1-3). The risk of death for those with OH was 2.2 times (95% CI: 1.5-3.4) higher than for those without OH. There was no significant interaction between OH and DM (online Table 4) for any of the outcomes, indicating that the association between OH and outcomes did not differ in those with and without DM.

Discussion

We studied the association between OH and vascular outcomes in this large, well-defined cohort of lacunar stroke survivors from the SPS3 trial and found that OH was associated with an increased risk of recurrent stroke, ischemic stroke, major vascular events, and all cause death. This association was not observed for hemorrhagic strokes and MI.

To date, this report is the first comprehensive examination of orthostatic BP drop and recurrent stroke and vascular events. Prior reports have largely examined incident events and have shown an association between OH and incident ischemic stroke[3] and also silent cerebrovascular

Table 1. *Baseline characteristics of participants according to categories of orthostatic blood pressure. Orthostatic hypotension (OH) defined by drop of SBP of 20 mm Hg or DBP of 10 mm Hg on changing from sitting to standing position during 1 or more follow-up visits*

	Overall (n = 2275)	No OH (n = 1394)	OH (n = 881)	*P* value
Demographics				
Age, years (mean, SD)	63.5 (10.8)	63.4 (10.8)	63.6 (10.8)	.70
Male	1445 (64%)	927 (67%)	518 (59%)	.0002
Race				.0002
White	1118 (49%)	640 (46%)	478 (54%)	
Black	313 (14%)	206 (15%)	107 (12%)	
Hispanic	794 (35%)	523 (38%)	271 (31%)	
Other/mixed	50 (2%)	25 (2%)	25 (3%)	
Region				<.0001
US	1011 (44%)	570 (41%)	441 (50%)	
Canada	232 (10%)	136 (10%)	96 (11%)	
Latin America	672 (30%)	455 (33%)	217 (25%)	
Spain	360 (16%)	233 (17%)	127 (14%)	
Health behaviors				
Smoking				.59
Current	455 (20%)	273 (20%)	182 (21%)	
Past	892 (39%)	541 (39%)	351 (40%)	
Never	928 (41%)	580 (42%)	348 (40%)	
Regular alcohol use	305 (13%)	174 (12%)	131 (15%)	.11
Physiologic measures				
Baseline SBP (mean, SD)	142 (19)	142 (18)	142 (19)	.55
Baseline DBP (mean, SD)	78 (11)	78 (10)	78 (11)	.47
Body mass index (mean, SD)	29.0 (6.9)	28.8 (5.6)	29.3 (8.6)	.13
Baseline OH	192 (8%)	85 (6%)	107 (12%)	<.0001
Baseline orthostatic symptoms	178 (8%)	98 (7%)	80 (9%)	.078
Health history				
Diabetes mellitus type 2	834 (37%)	489 (35%)	345 (39%)	.049
Hypertension history	2031 (89%)	1238 (89%)	793 (90%)	.36
MI	98 (4%)	41 (4%)	57 (5%)	.45
Angina	111 (5%)	39 (4%)	72 (6%)	.024
CHF	16 (.70%)	5 (.5%)	11 (.9%)	.25
CABG/PTCA/stent	92 (4%)	43 (4%)	48 (4%)	.74
COPD	55 (2%)	25 (2%)	30 (2%)	.99
Hyperlipidemia	1060 (47%)	443 (43%)	517 (50%)	.0007
Endarterectomy, etc.	16 (.70%)	5 (.5%)	11 (.9%)	.25
Pacemaker	1 (.04%)	0 (0%)	1 (.04%)	>.99
Peripheral vascular disease	72 (3%)	26 (3%)	46 (4%)	.12
Sleep apnea	80 (4%)	37 (4%)	43 (4%)	.90
Medication use				
Mean hypertension medicationsat baseline (SD)	1.6 (1.2)	1.6 (1.5)	1.7 (1.6)	.053
Statin use baseline	1602 (70%)	976 (70%)	626 (71%)	.60
Mean hypertension medications at follow-up (SD)	2.0 (1.3)	2.0 (1.3)	2.1 (1.3)	.062
Study parameters				
Higher BP target	1146 (50%)	669 (48%)	477 (54%)	.0042
Number of follow-up visits	11.6 (6.4)	10.4 (6.4)	13.6 (5.9)	<.0001
Loss to follow-up	44 (1.9%)	31 (2%)	13 (1.5%)	.21

infarcts.[4] Our findings on the association between OH and recurrent ischemic stroke, major vascular events, and all-cause mortality expand what is known on this topic. The issue of recurrent strokes is particularly relevant since the majority of incident stroke survivors are hypertensive and are typically on antihypertensive medications or are started on them after the stroke. We also note that the majority of participants with an orthostatic BP drop did not report orthostatic symptoms (59%).

Physiological adjustments to orthostatic stress have been studied previously.[5,16,17] Positional change from sitting or supine to standing leads to pooling of blood to the

Table 2. *Unadjusted event rates (95% CI) according to categories of orthostatic blood pressure. orthostatic hypotension (OH) defined by drop of SBP of 20 mm Hg or DBP of 10 mm Hg on changing from sitting to standing position during 1 or more follow-up visits*

	No OH		OH	
Outcomes	Events N (mean follow-up, years)	Rate Percent/person-year	Events N (mean follow-up, years)	Rate Percent/person-year
All stroke	101 (2.9)	2.5 (2.0, 3.0)	48 (3.7)	1.5 (1.1, 1.9)
Ischemic stroke	86 (2.9)	2.1 (1.7, 2.6)	41 (3.7)	1.2 (.89, 1.7)
Hemorrhagic stroke	15 (2.9)	.37 (.21, .58)	7 (3.7)	.21 (.085, .40)
Major vascular events	121 (2.9)	3.0 (2.5, 3.5)	61 (3.7)	1.9 (1.4, 3.4)
Myocardial infarction	22 (3.0)	.52 (.32, .76)	14 (3.8)	.42 (.23, .67)
All-cause death	75 (3.1)	1.8 (1.4, 2.2)	39 (3.8)	1.2 (.82, 1.6)

lower extremities, and, in the splanchnic and pulmonary circulations.[16,17] As a result, there is a decrease in venous return and ventricular filling. This causes a transient reduction in stroke volume, a slight fall in SBP, and a rise in DBP. This can activate high-pressure baroreceptors in the carotid sinus and aortic arch and low-pressure receptors in the heart and lungs, and can increase sympathetic outflow and decrease parasympathetic tone.[18-20] These changes lead to an increase in heart rate and peripheral vascular resistance. Increase in sympathetic activity caused by orthostatic stress can stimulate the Renin-angiotensin-aldosterone system which contributes to vasoconstriction.[5,16,17] Abnormalities disrupting this chain of responses can lead to OH.

In our sample with lacunar infarcts, the association of OH with recurrent stroke could be due to several mechanisms. Physiologically, cerebral small vessel disease is thought to occur due to arteriolar hyalinization of smaller perforating blood vessels in the brain.[21,22] Patients who already have these vascular changes in their small perforating brain vessels, are likely to have long standing HTN and arteriosclerosis.[23] In such condition, there is decreased arterial wall compliance leading to a reduced baroreceptor responsiveness or subsequent pooling of blood in the peripheral vascular system which can lead to exaggerated brain hypoperfusion due to orthostatic stress.[2,24] Procoagulant activation of cerebral microvascular endothelium has also been described in lacunar stroke which can be exaggerated with OH.[25,26] Diabetes, a well-established risk factor for stroke,[27] may also lead to OH through autonomic dysfunction and associated HTN as well as cardiac autonomic neuropathy.[28] We did not find any significant differences in relationship between OH and the risk of events by diabetes status. A different possibility is that patients with OH (especially symptomatic OH) may have had lower medication adherence due to side effects and hence higher stroke recurrence. Unfortunately, we did not collect adherence to BP medications systematically. The study did collect adherence to antiplatelet therapies and the adherence to these was 94%. Nevertheless, we are unable to answer whether a worse adherence to antihypertensive medications in patients with symptomatic OH played a role in the worse observed outcomes.[13]

We note that the hazard ratios in Cox models using the more liberal definition of OH (BP drop + symptoms) were attenuated for all stroke, ischemic stroke, and major vascular events when compared to models using the strict definition of OH (BP drop only). This may suggest that the presence of BP drop was a key marker of the

Table 3. *Hazard ratios (95% CI) of events by exposure defined as orthostatic hypotension (OH) defined by drop of SBP of 20 mm Hg or DBP of 10 mm Hg on changing from sitting to standing position during 1 or more follow-up visits. (reference is no OH)*

Outcomes	Model 1*	Model 2†	Model 3‡	Model 4§
All stroke	2.1 (1.3, 3.3)	2.0 (1.3, 3.3)	2.0 (1.2, 3.2)	1.8 (1.1, 3.0)
Ischemic stroke	2.1 (1.2, 3.4)	2.0 (1.2, 3.3)	1.9 (1.1, 3.2)	1.8 (1.0, 3.0)
Hemorrhagic stroke	2.2 (.64, 7.3)	2.6 (.75, 8.8)	2.5 (.71, 8.5)	2.2 (.63, 7.6)
Major vascular events	2.1 (1.4, 3.3)	2.1 (1.4, 3.3)	2.1 (1.3, 3.2)	1.9 (1.2, 2.9)
Myocardial infarction**	2.2 (.84, 5.6)	2.1 (.80, 5.4)	2.0 (.78, 5.4)	1.9 (.73, 5.1)
All-cause death	2.3 (1.4, 3.8)	2.4 (1.4, 4.0)	2.0 (1.2, 3.4)	1.9 (1.1, 3.2)

*Model 1: univariate.
†Model 2: +age, race, gender, region.
‡Model 3: +smoking, alcohol use, BL SBP, BL orthostatic hypotension.
§Model 4: +diabetes mellitus, history of hypertension, baseline number of hypertension medications, follow-up number of hypertension medications, hyperlipidemia at baseline, baseline angina, target BP group.
**Myocardial infarction models omit race due to the lack of events among some race groups.

Table 4. *Interaction between orthostatic hypotension and diabetes mellitus in fully adjusted model (model 4 from Table 3)*

Outcomes	*P* for interaction
All stroke	.96
Ischemic stroke	.78
Hemorrhagic stroke	.56
Major vascular events	.28
Myocardial infarction	.99
All-cause death	.79

Table 5. *Interaction between orthostatic hypotension and target blood pressure group of the trial in fully adjusted model (model 4 from Table 3)*

Outcomes	*P* for interaction
All stroke	.71
Ischemic stroke	.54
Hemorrhagic stroke	.56
Major vascular events	.96
Myocardial infarction	.20
All-cause death	.75

sympathetic dysregulation that led to worse outcomes. This did not hold for all-cause mortality. The HR for all outcomes with both definitions of OH were however consistent and comparable.

OH is strongly associated with risk of incident cardiovascular complications, including MI, heart failure, stroke, and all-cause mortality.[2,5,16] However, OH was not associated with MI in our study. This could reflect smaller number of MI events related to more aggressive management of vascular risk factors in study group compared to patients with OH who never had stroke. Concurrent use of multiple antihypertensive agents is also linked with OH, however, impact of individual drug class on OH is unclear with inconsistency in findings between different studies.[5,6,29] In our study sample, though not statistically significant (P = .053), higher number of antihypertensives were used in OH group.

The strengths of our study are the large number of well-defined lacunar strokes (using clinical and neuroimaging criteria), the standardized measurement of BP, and the standardized assessment of outcomes. We acknowledge that this is a retrospective cohort. The selection bias inherent to clinical trials (ie healthier patients are more likely to participate) applies, and furthermore, the trial was not designed to address the study question specifically. One consequence of this is that the available data does not allow analysis of outcomes by the presence or absence of heart rate increase as an additional aspect of the orthostatic response. We also cannot comment on any differences in outcomes between nonneurogenic and traditional neurogenic OH such as those caused by pure autonomic failure or multisystem atrophy in our analyses as patients with these significant illnesses were excluded from the SPS3 study. We acknowledge that there is a potential for unmeasured confounding, as is true with any analysis examining observational data. In order to assess the extent of unmeasured confounders, we computed the E-value for the hazard ratio for primary outcome (all stroke) and its 95% CI: 3.1 (1.4, 5.5). This suggests that the observed hazard ratio of 1.8 could be attenuated by an unmeasured confounder that was associated with both the orthostatic HTN and stroke by a relative risk of 3.1 each, beyond the confounders included in our model. Thus, results should be interpreted in this context.

Future work should address whether certain classes of antihypertensive medications were associated with OH and the impact of specific medication classes on the association between OH and outcomes, which could have important implications for clinical practice. We are unable to answer this question since medications were adjusted at each visit to achieve assigned target. Antihypertensive drugs have differential effects on BP variability. We acknowledge that this study did not examine the extent of BP variability and whether BP variability modified the relationship between OH and vascular outcomes in this cohort. Another limitation is that the number of follow-up visits were significantly higher in the OH group. Consequently, this could lead to ascertainment of more outcomes in the OH group. In order to mitigate this, we used OH as a time varying covariate in our analysis. We believe that this contributes to the different results between the rates versus Cox models. Nevertheless, we do not think that outcomes were necessarily missed in the non-OH group. The SPS3 trial was a carefully monitored trial and there was close supervision of study sites. The outcomes were ascertained systematically and were hard outcomes, ie stroke, MI, and mortality that were centrally adjudicated by a committee external to the study team. Furthermore, the loss to follow-up was 2% and the loss to follow-up was similar between the 2 groups (Table 1).

While SPS3 measured OH from a seated to standing position, it is sometimes measured by comparing supine versus standing BP in a hospital (in-patient) setting. The latest ACC HTN guidelines define OH as measured from a seated versus standing position.[30] The SPS3 was a multicenter international trial. OH was measured from a seated to upright position to achieve consistency in measurement across clinics. A number of clinics were not equipped with an examination table to have the patient supine so rather than having OH measured in different ways across clinic, the measurement was standardized from seated to upright for all clinics. This measurement of OH as from a seated to standing position was therefore more specific (and less sensitive) and also identified the more severe cases of OH.

We considered practice implications of our research. Since this is a retrospective study based on secondary

analysis of clinical trial data, we do not know if evaluation and management of OH will attenuate the observed increased risk of cardiovascular events in stroke survivors with OH. We infer that our results provide Level 3 evidence (retrospective cohort) that OH maybe a prognostic factor in the outcomes of patients with lacunar infarcts. A similar association is found in the general population.[2-4]

Conclusion

OH was associated with increased recurrent stroke risk, vascular events, and all-cause death in this large cohort of lacunar stroke patients in the SPS3 study, (Level 3 evidence). Our results raise the question as to whether clinical practice should routinely measure orthostatic BP during outpatient visits in stroke survivors since many participants with OH did not report symptoms. Furthermore, one should consider whether future clinical trials on HTN should not only treat BP to target but also treat to avoid both asymptomatic and symptomatic OH.

Sources of Funding

The SPS3 was funded by a grant from the National Institute of Neurological Disorders and Stroke (U01 NS38529-04A1).

Disclosures

None.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.04.009.

References

1. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160-2236.
2. Eigenbrodt ML, Rose KM, Couper DJ, et al. Orthostatic hypotension as a risk factor for stroke: The atherosclerosis risk in communities (ARIC) study, 1987-1996. Stroke 2000;31:2307-2313.
3. Yatsuya H, Folsom AR, Alonso A, et al. Postural changes in blood pressure and incidence of ischemic stroke subtypes: the ARIC study. Hypertension 2011;57:167-173.
4. Eguchi K, Kario K, Hoshide S, et al. Greater change of orthostatic blood pressure is related to silent cerebral infarct and cardiac overload in hypertensive subjects. Hypertens Res 2004;27:235-241.
5. Feldstein C, Weder AB. Orthostatic hypotension: a common, serious and underrecognized problem in hospitalized patients. J Am Soc Hypertens 2012;6:27-39.
6. Kamaruzzaman S, Watt H, Carson C, et al. The association between orthostatic hypotension and medication use in the british women's heart and health study. Age Ageing 2010;39:51-56.
7. Benavente OR, Coffey CS, Conwit R, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet 2013;382:507-515.
8. Benavente OR, White CL, Pearce L, et al. The secondary prevention of small subcortical strokes (sps3) study. Int J Stroke 2011;6:164-175.
9. Pergola PE, White CL, Graves JW, et al. Reliability and validity of blood pressure measurement in the secondary prevention of small subcortical strokes study. Blood Press Monit 2007;12:1-8.
10. White CL, Pergola PE, Szychowski JM, et al. Blood pressure after recent stroke: baseline findings from the secondary prevention of small subcortical strokes trial. Am J Hypertens 2013;26:1114-1122.
11. Pergola PE, White CL, Szychowski JM, et al. Achieved blood pressures in the secondary prevention of small subcortical strokes (sps3) study: challenges and lessons learned. Am J Hypertens 2014;27:1052-1060.
12. White CL, Szychowski JM, Roldan A, et al. Clinical features and racial/ethnic differences among the 3020 participants in the secondary prevention of small subcortical strokes (sps3) trial. J Stroke Cerebrovasc Dis 2013;22:764-774.
13. Benavente OR, Hart RG, McClure LA, et al. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med 2012;367:817-825.
14. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association. Stroke 2018;49:e46-e110.
15. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the e-value. Ann Intern Med 2017;167:268-274.
16. Benvenuto LJ, Krakoff LR. Morbidity and mortality of orthostatic hypotension: implications for management of cardiovascular disease. Am J Hypertens 2011;24:135-144.
17. Gupta D, Nair MD. Neurogenic orthostatic hypotension: chasing "the fall". Postgrad Med J. 2008;84:6-14.
18. Ziegler MG, Lake CR, Kopin IJ. The sympathetic-nervous-system defect in primary orthostatic hypotension. N Engl J Med 1977;296:293-297.
19. Thompson WO, Thompson PK, Dailey ME. The effect of posture upon the composition and volume of the blood in man. J Clin Invest 1928;5:573-604.
20. Maw GJ, Mackenzie IL, Taylor NA. Redistribution of body fluids during postural manipulations. Acta Physiol Scand 1995;155:157-163.
21. Mathias CJ. Orthostatic hypotension: causes, mechanisms, and influencing factors. Neurology 1995;45:S6-S11.
22. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. Lancet Neurol 2013;12:483-497.
23. Ejaz AA, Haley WE, Wasiluk A, et al. Characteristics of 100 consecutive patients presenting with orthostatic hypotension. Mayo Clin Proc 2004;79:890-894.
24. Raiha I, Luutonen S, Piha J, et al. Prevalence, predisposing factors, and prognostic importance of postural hypotension. Arch Intern Med 1995;155:930-935.
25. Guazzi M, Lenatti L, Tumminello G, et al. Effects of orthostatic stress on forearm endothelial function in normal subjects and in patients with hypertension, diabetes, or both diseases. Am J Hypertens 2005;18:986-994.
26. Knottnerus IL, Ten Cate H, Lodder J, et al. Endothelial dysfunction in lacunar stroke: a systematic review. Cerebrovasc Dis 2009;27:519-526.

27. Hill MD. Stroke and diabetes mellitus. Handb Clin Neurol 2014;126:167-174.
28. Fisher VL, Tahrani AA. Cardiac autonomic neuropathy in patients with diabetes mellitus: current perspectives. Diabetes Metab Syndr Obes 2017;10:419-434.
29. Di Stefano C, Milazzo V, Totaro S, et al. Orthostatic hypotension in a cohort of hypertensive patients referring to a hypertension clinic. J Hum Hypertens 2015;29:599-603.
30. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College Of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension 2018;71:1269-1324.