ORIGINAL ARTICLE

Blood Pressure After Recent Stroke: Baseline Findings From the Secondary Prevention of Small Subcortical Strokes Trial

Carole L. White,[1*] Pablo E. Pergola,[2*] Jeff M. Szychowski,[3#] Robert Talbert,[4*] Amin Cervantes-Arriaga,[5] Heather D. Clark,[6] Oscar H. Del Brutto,[7] Ivan Esteban Godoy,[8] Michael D. Hill,[9] Antoni Pelegrí,[10] Craig R. Sussman,[11] Addison A. Taylor,[12] José Valdivia,[13] Dave C. Anderson,[14] Robin Conwit,[15] and Oscar R. Benavente[16*] for the SPS3 Investigators

BACKGROUND
Hypertension is the most powerful risk factor for stroke. The aim of this study was to characterize baseline blood pressure in participants in the Secondary Prevention of Small Subcortical Strokes trial.

METHODS
For this cross-sectional analysis, participants were categorized by base-line systolic blood pressure (SBP) < 120, 120–139, 140–159, 160–179, and ≥ 180 mm Hg and compared on demographic and clinical characteristics. Predictors of SBP < 140 mm Hg were examined.

RESULTS
Mean SBP was 143 ± 19 mm Hg while receiving an average of 1.7 anti-hypertensive medications; SBP ≥ 140 mm Hg for 53% and ≥ 160 mm Hg for 18% of the 3,020 participants. Higher SBP was associated with a history of hypertension and hypertension for longer duration (both $P < 0.0001$). Higher SBPs were associated with more extensive white matter disease on magnetic resonance imaging ($P < 0.0001$). There were significant differences in entry-level SBP when participants were categorized by race and region (both $P < 0.0001$). Black participants were more likely to have SBP ≥ 140 mm Hg. Multivariable logistic regression showed an independent effect for region with those from Canada more likely (odds ratio = 1.7; 95% confidence interval, 1.29, 2.32) to have SBP < 140 mm Hg compared with participants from United States.

CONCLUSIONS
In this cohort with symptomatic lacunar stroke, more than half had uncontrolled hypertension at approximately 2.5 months after stroke. Regional, racial, and clinical differences should be considered to improve control and prevent recurrent stroke.

CLINICAL TRIALS REGISTRATION
Trial Number NCT00059306

Keywords: blood pressure control; blood pressure; ethnicity; hypertension; ischemic stroke; lacunar stroke; risk factors; stroke prevention; white matter disease.

doi:10.1093/ajh/hpt076

Hypertension is the single most powerful and prevalent risk factor for stroke, particularly for stroke associated with cerebral small vessel disease. Although a reliable body of evidence has shown that blood pressure (BP) lowering is effective for secondary stroke prevention,[1–7] there is a paucity of randomized data addressing the optimal level to which BP should be reduced to prevent recurrence. Furthermore, optimal target levels of BP for secondary prevention may not be identical for all etiologies of ischemic stroke.[8,9] Although evidence is lacking from randomized controlled trials about the ideal target of systolic blood pressure (SBP) to delay or prevent stroke recurrence and delay cognitive decline, guidelines advocate SBP should be aimed at or below 140 mm Hg in high risk individuals, which would include those with a history of stroke.[10–12]

Correspondence: Pablo E. Pergola (ppergola@raparesearch.com).

*SPS3 Coordinating Center
#SPS3 Statistical Center

[1]School of Nursing, University of Texas Health Sciences Center at San Antonio, San Antonio, TX; [2]Department of Medicine, University of Texas Health Sciences Center at San Antonio and Renal Associates PA, San Antonio, TX; [3]Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL; [4]College of Pharmacy, University of Texas at Austin, Austin, TX; [5]Neurodegenerative Research Unit, National Institute of Neurology and Neurosurgery, Mexico City, Mexico; [6]Department of Medicine, University of Ottawa and the Ottawa Hospital, Ottawa, Canada; [7] School of Medicine, Universidad Espíritu Santo, Ecuador and Department of Neurological Sciences, Hospital-Clínica Kennedy, Guayaquil, Ecuador; [8]Department of Medicine, Pontifica Universidad Católica de Chile, Santiago, Chile; [9]Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada; [10]Nephrology Department, Hospital Sagrat Cor, Barcelona, Spain; [11]Divisions of General Internal Medicine and Endocrinology/Metabolism, Vanderbilt University Medical Center, Nashville, TN; [12]Division of Hypertension and Clinical Pharmacology, Section on Cardiovascular Research, Department of Medicine, Baylor College of Medicine, Houston, TX; [13]Department of Medicine, Hospital Alberto Sabogal, Callao-Peru, Lima, Peru; [14]Hennepin County Medical Center, University of Minnesota Medical School, Minneapolis, MN; [15]NINDS, Office of Clinical Research, Bethesda, MD; and [16]Division of Neurology, Department of Medicine, Brain Research Center, University of British Columbia, Vancouver, Canada.

The Secondary Prevention of Small Subcortical Strokes (SPS3) study[13] was conducted to address the question of optimal BP targets for secondary stroke prevention and prevention of cognitive decline. The cross-sectional analyses presented here were undertaken to characterize BP control in participants in the SPS3 trial by BP levels at trial entry, prior to randomization, and to examine for ethnic and regional BP differences.

METHODS

The design of the SPS3 study has been published elsewhere.[13,14] Briefly, the study is an international multisite trial that was conducted in 81 sites in the United States, Latin America (Mexico, Ecuador, Peru, Chile, and Argentina), Canada, and Spain between May 2003 and April 2012. Participants (n = 3,020) who were aged ≥ 30 years with a recent lacunar stroke (≤ 6 months) and radiological confirmation were randomized in a 2 × 2 factorial design to one of two levels of SBP control and to one of two regimens of antiplatelet therapy. Both normotensive and hypertensive patients were eligible. The primary outcome was time to first recurrent stroke, and secondary outcomes were cognitive decline and major vascular events. The institutional review boards or ethics committees of all participating centers approved the SPS3 study, and all patients provided written informed consent.

Patients underwent 2 study visits prior to randomization for collection of all baseline data and determination of eligibility. Baseline data included BP measurement, the results of the neuroimaging and laboratory blood tests, cognitive and functional assessments, and medical history, including current medications. The first visit was completed at least 1 week after the qualifying stroke and after discharge from the hospital. The second visit was completed at least 1 week following the first visit to allow for separation in time of the BP measurements. Blood pressure was measured following a standardized protocol at the 2 prerandomization visits, during which patients continued on their usual BP–lowering medications. Adjustments were allowed during screening and before randomization. All sites were provided with an automated electronic device (Colin 8800C) for BP measurement.[15] At the initial visit, BP was measured in both arms. The right arm was used for BP measurement at all subsequent visits unless the SBP was at least 10 mm Hg higher in the left arm. In this case, the left arm was used for subsequent measurements. Blood pressure was measured 3 times in the seated position at each of the 2 prerandomization visits, and the average of these 6 measurements was defined as the baseline BP and forms the basis for the cross-sectional analyses presented here.

Statistical analyses

Baseline SBP was categorized according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines[11] to include the following categories: normal (< 120), prehypertension (120–139), stage 1 hypertension (140–159), and stage 2 (160–179; ≥ 180). Note that the BP measurements presented here reflect community management of BP after stroke at 81 clinical centers prior to study entry and management. There was no washout period, and the majority of patients were receiving treatment for hypertension at the time of their baseline BP measurements.

Baseline characteristics are presented as frequencies (percentages) and means ± SDs for categorical and quantitative measures, respectively. Mantel-Haenszel χ^2 tests were used to investigate linear trends across the SBP categories for categorical characteristics. General linear models with linear contrasts were used to investigate linear trends across the SBP categories for quantitative characteristics. Linear contrasts provide a formal mechanism for testing for a trend across the 5 ordinal SBP categories. Variables used to characterize BP at study entry, including SBP categories, mean BP, and duration of hypertension, were then examined by race/ethnicity and by geographic region. The χ^2 tests of general association, analysis of variance, and Kruskal-Wallis tests were used, as appropriate, for categorical and quantitative variables, respectively. All tests of significance were 2-sided and unadjusted P values are presented. Because of multiple comparisons, an alpha level of < 0.01 was selected to indicate statistical significance.

Categorization of the 81 sites into regions was done a priori and based on similarities and differences in geography, culture, and healthcare systems. The 4 regions are the United States, Latin America, Spain, and Canada. To examine the independent effect of geographic region on hypertensive status, baseline SBP was categorized as SBP < 140 vs. SBP ≥ 140 mm Hg. All baseline variables were entered simultaneously as covariates in a multivariable logistic regression model. These covariates include baseline demographics identified as being significantly associated with linear trends in the baseline SBP and also variables thought to be clinically relevant, thus requiring consideration in the model. Where multiple measurements were highly correlated with one another (e.g., diabetes, glucose, and glycosylated hemoglobin), only 1 of the related variables was included in the regression model. For brevity, only regional effects and the statistically significant covariates are presented. Odds ratios and 95% confidence intervals are presented. SAS version 9.2 (SAS Institute Inc, Cary, NC) was used for all statistical analyses.

RESULTS

More than half of the cohort (n = 3,020) had a baseline SBP ≥ 140 mm Hg at approximately 2.5 months after their qualifying stroke (Table 1). Almost one-fifth (18%) had baseline SBP values consistent with stage 2 (≥ 160 mm Hg) hypertension despite treatment (95% treated). Subjects with higher SBP entered the study earlier than those in lower SBP categories ($P < 0.01$). The mean ± SD systolic and diastolic BPs for the overall cohort were 143 ± 19 mm Hg and 78 ± 11, respectively, ranging from a low of 113 ± 6 mm Hg systolic and 65 ± 7 mm Hg diastolic to a high of 192 ± 12 mm Hg systolic and 96 ± 12 mm Hg diastolic. Wider pulse pressure, history of hypertension, and a longer duration of

Table 1. Characteristics of study participants stratified by SBP at study entry

Characteristic	Overall (n = 3,020)	Baseline SBP					P value
		< 120 (n = 230)	120–139 (n = 1,191)	140–159 (n = 1,049)	160–179 (n = 431)	≥180 (n = 119)	
Days since stroke, mean ± SD	76.4±47.1	81.5±48.2	77.1±47.5	76.2±46.6	74.5±46.7	68.4±44.8	< 0.01
Age, mean years ± SD	63.3±10.8	62.8±10.7	62.7±10.7	63.8±10.8	64.2±10.5	63.3±11.6	0.33
Male, n (%)	1,902 (63.0)	142 (61.7)	803 (67.4)	653 (62.3)	245 (56.8)	59 (49.6)	< 0.0001
Blood pressure variables							
History of hypertension, n (%)	2,264 (75.0)	137 (59.6)	792 (66.5)	844 (80.5)	381 (88.4)	110 (92.4)	< 0.0001
Duration of hypertension, mean years ± SD[a]	9.6±9.6	7.7±8.0	8.8±9.3	9.5±9.1	11.0±10.7	12.9±11.2	< 0.0001
Hypertensive by SPS3 criteria,[b] (n) %	2,708 (89.7)	132 (57.4)	977 (82.0)	1,049 (100)	431 (100)	119 (100)	< 0.0001
Mean number of antihypertensive medications, ± SD	1.7±1.2	1.4±1.2	1.5±1.1	1.7±1.2	2.0±1.3	2.3±1.2	< 0.0001
No antihypertensive medications, n (%)	463 (15.3)	55 (23.9)	237 (19.9)	144 (13.7)	23 (5.3)	4 (3.4)	< 0.0001
Mean SBP (mm Hg) ± SD	143.0±18.8	113.0±5.5	130.5±5.5	148.4±5.8	167.0±5.6	192.2±11.5	< 0.0001
Mean DBP (mm Hg) ± SD	78.3±10.6	64.6±6.7	73.9±7.2	80.8±8.1	87.0±9.7	96.1±12.2	< 0.0001
DBP > 90mm Hg, n (%)	459 (15.2)	0 (0)	37 (3.1)	172 (16.4)	168 (39.0)	82 (68.9)	< 0.0001
Mean pulse pressure (mm Hg) ± SD	64.7±14.0	48.4±6.6	56.5±7.4	67.6±8.6	80.0±10.0	96.0±14.6	< 0.0001
Mean heart rate (BPM) ± SD	72.4±11.9	72.8±11.4	72.5±11.2	72.4±12.2	71.5±13.1	72.8±13.4	0.77
Medical and social history, (n) %							
Hyperlipidemia	1,471 (48.7)	117 (50.9)	563 (47.3)	515 (49.1)	221 (51.3)	55 (44.2)	0.64
Statin use	2,080 (68.9)	173 (75.2)	836 (70.2)	717 (68.4)	279 (64.7)	75 (63.0)	< 0.01
Diabetes	1,106 (36.6)	89 (38.7)	405 (34.0)	373 (35.6)	194 (45.0)	43 (37.8)	0.02
Insulin use	320 (10.6)	31 (13.5)	100 (8.4)	113 (10.8)	58 (13.5)	18 (15.1)	0.02
Ischemic heart disease	317 (10.5)	20 (8.7)	119 (10.0)	113 (10.8)	52 (12.1)	13 (10.9)	0.17
Prior symptomatic small subcortical stroke/TIA	448 (14.8)	37 (16.1)	168 (14.1)	159 (15.2)	67 (15.5)	17 (14.3)	0.80
Intermittent claudication/peripheral vascular disease	95 (3.2)	9 (3.9)	37 (3.1)	25 (2.4)	16 (3.7)	8 (6.7)	0.38
Current smoking	617 (20.4)	52 (22.6)	244 (20.5)	202 (19.3)	95 (22.0)	24 (20.2)	0.15
Alcohol use (≥ 7 drinks/week)	386 (12.8)	31 (13.5)	159 (13.4)	136 (13.0)	46 (11.1)	12 (10.1)	0.18
Selected clinical measurements, mean ± SD							
Glucose (mg/dl)	125.6±55.0	125.7±53.7	123.5±52.0	125.0±56.4	132.6±60.1	126.2±53.6	0.43
Glycosylated hemoglobin (%) (diabetics only)	8.3±2.2	8.3±2.3	8.3±2.3	8.4±2.3	8.1±2.1	8.7±2.1	0.51
Creatinine	0.96±0.26	0.92±0.22	0.95±0.24	0.95±0.26	1.00±0.29	1.01±0.29	< 0.0001
eGFR	80.2±18.9	82.5±17.6	81.7±18.4	80.3±19.3	76.4±18.4	75.0±20.9	< 0.0001

(Continued)

Table 1. Continued

Characteristic	Baseline SBP						
	Overall (n = 3,020)	< 120 (n = 230)	120–139 (n = 1,191)	140–159 (n = 1,049)	160–179 (n = 431)	≥180 (n = 119)	*P* value
Total cholesterol (mg/dl)	187.9±47.1	175.2±44.0	187.2±48.5	189.7±45.9	190.2±47.2	195.9±44.2	< 0.0001
LDL cholesterol (mg/dl)	112.3±39.8	102.5±36.3	111.5±40.3	113.9±38.5	113.2±40.4	122.0±47.2	< 0.0001
HDL cholesterol (mg/dl)	45.4±18.4	42.8±13.7	45.0±19.0	46.3±20.3	45.2±13.8	46.6±16.5	0.07
Triglycerides (mg/dl)	164.6±114.2	156.6±82.3	164.2±113.9	163.8±122.8	172.4±114.2	162.3±90.0	0.47
Weight (Kg)	81.1±18.4	77.6±17.5	81.6±17.9	81.6±18.8	80.6±19.0	79.7±19.5	0.46
BMI	29.1±6.8	27.8±5.3	29.0±7.6	29.3±6.3	29.6±6.6	28.8±5.9	0.10
Waist circumference (cm)c	99.0±13.8	98.1±13.4	98.8±13.9	99.2±13.5	99.8±14.3	97.5±16.0	0.99
MRI characteristics							
Multiple (> 1) subcortical infarcts, n (%)	1,189 (39.6)	77 (33.5)	424 (35.8)	436 (41.8)	191 (44.5)	61 (51.3)	< 0.0001
Moderate to severe white matter abnormalities (ARWMA), n (%)	1,480 (49.8)	102 (44.5)	503 (43.3)	532 (51.5)	261 (61.1)	82 (69.5)	< 0.0001
Functional recovery							
Mean Barthel index ± SD	95.4±9.7	94.6±11.5	96.0±9.2	95.1±9.7	94.9±10.7	95.8±7.5	0.52
Modified Rankin scale (0–1), n (%)	2,011 (66.6)	150 (65.2)	807 (67.8)	695 (66.3)	287 (66.6)	72 (60.5)	0.37
Depressed, n (%)	528 (19.0)	39 (18.9)	203 (18.3)	172 (17.9)	82 (20.8)	32 (29.9)	0.049
CASI score above 90, n (%)	1,328 (44.6)	96 (42.3)	555 (47.1)	455 (44.1)	177 (41.6)	45 (38.5)	0.07

Barthel Index scored from 0 to 100 with higher scores indicating better functional ability. Modified Rankin scale of 0 to 1 indicates normal to near-normal recovery. CASI score from 0 to 100 with higher scores indicating better cognitive function.

Abbreviations: ARWMC, age-related white matter changes scale[16]; BMI, body mass index; CASI, Cognitive Abilities Screening Instrument[19]; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

aDocumented years of hypertension if available, otherwise self report.

bClassified as hypertensive by SPS3 criteria if one or both of following met: (a) average blood pressure from the 2 consecutive SPS3 visits was ≥ 140mm Hg systolic or ≥ 90mm Hg diastolic or (b) definite history of hypertension prior to the qualifying stroke and on antihypertensive medication at the time of visit.

cNot collected at trial initiation and available for 1,358 patients.

diagnosed hypertension were associated with higher SBP (all $P < 0.0001$). Those in the SBP ≥ 180 group had a mean hypertension duration of 13 ± 11 years, and > 90% reported a history of hypertension.

Medical and social history was not significantly different across SBP categories, and 15% of the cohort had a symptomatic lacunar stroke or transient ischemic attack prior to the qualifying stroke. Higher creatinine and lower estimated glomerular filtration rate were associated with higher SBP (both $P < 0.0001$). Those in the highest SBP categories were least likely to report taking lipid-lowering medications at study entry ($P < 0.01$) and also exhibited the highest total cholesterol and low-density lipoprotein cholesterol (both $P < 0.0001$).

Multiple subcortical infarcts and moderate to severe white matter disease by magnetic resonance (MRI)[16] were associated with higher levels of SBP (both $P < 0.0001$). Functional status was not associated with levels of SBP (measured by the Barthel Index,[17] the modified Rankin scale,[18] and baseline cognitive status[19]). The percentage reporting depression[20] ranged from 19% in those with SBP < 140 mm Hg to 30% in the group with the highest baseline SBP ($P = 0.049$).

Overall, participants were taking an average of 1.7 ± 1.2 antihypertensive medications at baseline, from a low of 1.4 ± 1.2 in the < 120 SBP group to a high of 2.3 ± 1.2 in the

≥ 180 SBP group. A small percentage of participants (15% overall) reported taking no antihypertensive medications at study entry, and the percentage decreased significantly with higher SBP ($P < 0.0001$). Figure 1 shows the distribution of antihypertensive medications at study entry by SBP levels. With higher SBP levels there were significantly increased proportions of patients taking antihypertensive medications in every class (all $P < 0.001$). Regardless of SBP category, more than half of the participants reported taking angiotensin converting enzyme (ACE) inhibitors at study entry, and an even higher percentage of patients were taking either an ACE inhibitor or an angiotensin receptor blocker. The percentage of patients taking diuretics ranged from a low of 28% in the lowest SBP group to 50% for those in the ≥ 180 SBP group. In those patients taking more than 1 agent, the most common combination of antihypertensive agents was a diuretic and ACE inhibitor. This ranged from 38% to 46% across the SBP groups.

To further characterize this multiracial/multiethnic international cohort, we examined entry-level BP by race/ethnicity and by geographic region. There were clear differences in entry-level BP and history of hypertension by race/ethnicity (Table 2; both $P < 0.0001$). Black participants were more likely to report a history of hypertension prior to their qualifying stroke, to enter the trial with uncontrolled
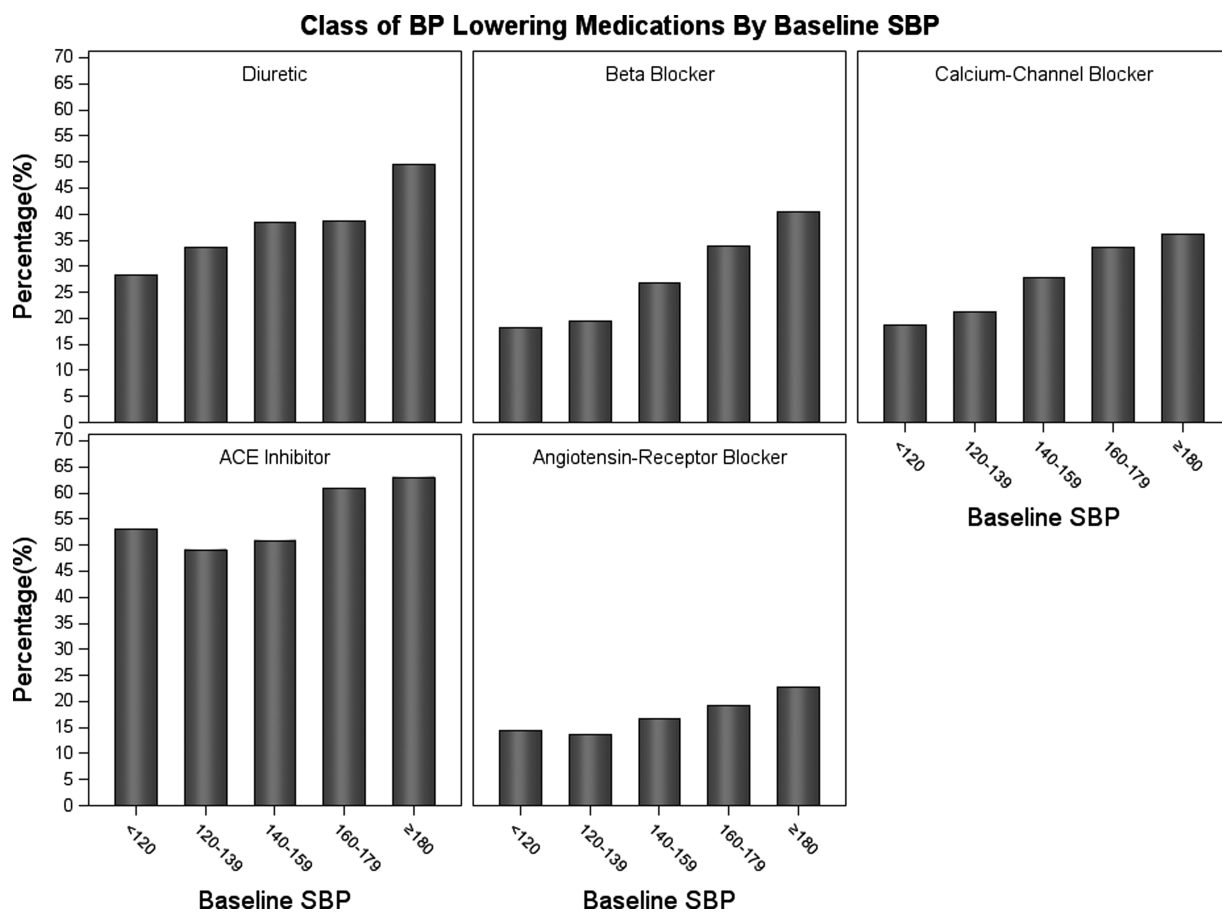
Figure 1. Distribution of antihypertensive medications by systolic blood pressure (SBP) group. *P* for trend: all *P* < 0.001.

Table 2. Baseline blood pressure by race/ethnicity

Blood Pressure Characteristics	Overall (n = 3,020)	Non-Hispanic White (n = 1,538)	Hispanic (n = 916) NA Non-NA (n = 222)	(n = 694)	Non-Hispanic Black (n = 492)	*P* value
Baseline SBP, n (%)						< 0.0001
< 120	230 (7.6)	127 (8.3)	8 (3.6)	63 (9.1)	27 (5.5)	
120–139	1191 (39.4)	651 (42.3)	95 (42.8)	250 (36.0)	165 (33.5)	
140–159	1,049 (34.7)	529 (34.4)	77 (34.7)	237 (34.2)	182 (37.0)	
160–179	431 (14.3)	196 (12.7)	33 (14.9)	105 (15.1)	88 (17.9)	
≥ 180	119 (3.9)	35 (2.3)	9 (4.1)	39 (5.6)	30 (6.1)	
Mean SBP ± SD	143.0±18.8	141.0±17.2	144.5±17.2	144.3±20.8	146.7±19.9	< 0.0001
Mean DBP ± SD	78.3±10.6	77.1±9.9	78.5±9.2	78.6±11.5	81.7±11.6	< 0.0001
History of hypertension, n (%)	2,264 (75.0)	1,074 (69.8)	170 (76.6)	530 (76.4)	428 (87.0)	< 0.0001
Mean duration of hypertension ± SD	9.6±9.6	9.4±9.7	9.2±9.5	9.2±9.4	10.6±9.7	0.24
Mean number of antihypertensive medications ± SD	1.7±1.2	1.6±1.2	1.7±1.2	1.4±0.9	2.1±1.2	< 0.0001

There were 74 participants who reported their race as American Indian/Alaskan Native, Asian/Pacific Islander, or "other. Because of the small numbers, and heterogeneity, this group is not included.

Abbreviations: DBP, diastolic blood pressure; NA, North America; SBP, systolic blood pressure.
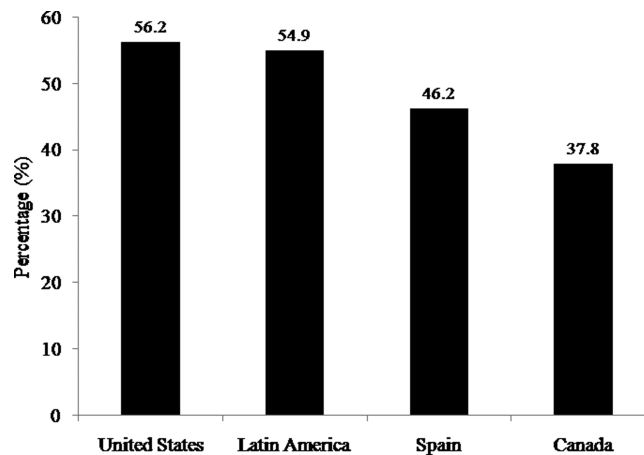
Figure 2. Percentage of all patients entered in the trial by region with baseline systolic blood pressure ≥ 140 mm Hg.

hypertension (SBP ≥ 140 mm Hg), and to be taking more antihypertensive medications. There were regional differences in percentages of patients with SBP ≥ 140 mm Hg at baseline (Figure 2) and in history and duration of hypertension, as well as mean number of antihypertensive medications at study entry (Table 3; all *P* < 0.001). To further examine this specific effect of geographic region, we undertook a multivariable logistic regression. Using the United States as a reference, participants from Canada were 1.73 times (95% confidence interval, 1.29, 2.32) more likely to enter the trial with SBP < 140 mm Hg compared with those from the United States, adjusted for history and duration of hypertension as well as number of medications and potentially confounding medical and demographic variables (Table 4).

DISCUSSION

Hypertension is quantitatively the most important risk factor for stroke, and achieving BP control is an essential therapeutic intervention to prevent recurrence. Although there were no BP criteria for trial entry, the cohort was dominated by those with hypertension. Approximately 75% reported a history of hypertension prior to their qualifying stroke, similar to the Prevention Regimen for Effectively Avoiding Second Strokes trial.[21] In contrast to that trial where 41% of patients were classified as hypertensive (median of 15 days after their index stroke),[22] SBP was ≥ 140 mm Hg in > 50% of this group at approximately 2.5 months after the qualifying stroke despite the majority (85%) of patients taking antihypertensive medications. This finding is consistent with

Table 3. Baseline blood pressure by geographic region of participation

Blood Pressure Characteristics	Overall (n = 3,020)	United States (n = 1,677)	Canada (n = 283)	Latin America (n = 694)	Spain (n = 366)	P value
Baseline SBP, n (%)						< 0.0001
< 120	230 (7.6)	96 (5.7)	35 (12.4)	63 (9.1)	36 (9.8)	
120–139	1,191 (39.4)	639 (38.1)	141 (49.8)	250 (36.0)	161 (44.0)	
140–159	1,049 (34.7)	615 (36.7)	72 (25.4)	236 (34.0)	126 (34.4)	
160–179	431 (14.3)	253 (15.1)	32 (11.3)	106 (15.3)	40 (10.9)	
≥ 180	119 (3.9)	74 (4.4)	3 (1.1)	39 (5.6)	3 (0.82)	
Mean SBP ± SD	143.0 ± 18.8	144.2 ± 18.5	137.4 ± 17.0	144.3 ± 20.8	139.3 ± 15.9	< 0.0001
Mean DBP ± SD	78.3 ± 10.6	78.7 ± 10.6	75.7 ± 10.0	78.6 ± 11.5	78.0 ± 9.3	< 0.0001
History of hypertension, n (%)	2,264 (75.0)	1,335 (79.6)	185 (65.4)	530 (76.4)	214 (58.5)	< 0.0001
Mean duration of hypertension ± SD	9.6 ± 9.6	10.2 ± 10.0	7.9 ± 8.4	9.2 ± 9.5	7.7 ± 8.0	< 0.001
Mean number of antihypertensive medications ± SD	1.7 ± 1.2	1.9 ± 1.3	1.6 ± 1.2	1.3 ± 0.9	1.3 ± 1.0	< 0.0001

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 4. Independent predictors of systolic blood pressure < 140 at study entry

Significant Independent Predictors	Adjusted Odds Ratio (95% Confidence Interval)
Region[a]	
United States	Ref
Canada	1.73 (1.29–2.32)
Latin America	1.05 (0.75–1.46)
Spain	1.12 (0.85–1.48)
History of hypertension	1.92 (1.54–2.39)
Years of hypertension	0.99 (0.98–1.00)
Number of antihypertensive medications at baseline	0.87 (0.80–0.94)

[a]Adjusted for all significant associations as seen above and race/ethnicity, time since stroke, age, gender, history of hyperlipidemia, diabetes, ischemic heart disease, and stroke/transient ischemic attack prior to qualifying stroke, current smoking, alcohol, creatinine, estimated glomerular filtration rate, and weight.

other publications reporting uncontrolled hypertension after stroke.[23,24] This may reflect the ongoing uncertainty about when and how aggressively BP treatment should begin after acute stroke, with limited data to guide practice.[25,26] The American Stroke Association guidelines support BP–lowering therapy as soon as 24 hours after acute ischemic stroke[27,28] but do not define a timeline for achieving the goal.

There were significant differences in BP at baseline by region of participation. The percentage of patients with SBP ≥ 140 mm Hg was higher in participants from the United States (56%) and Latin America (55%) in contrast to 46% in those from Spain and 38% in those from Canada. Baseline BP was measured according to a standardized protocol, so these differences cannot be attributed to differing measurement techniques across regions. The higher baseline control rates seen in Canada, and perhaps Spain, may reflect the Canadian

universally accessible, publicly funded healthcare system compared with the more limited insurance system existing in the United States.[29] The differences between Canada and the United States are in contrast to a previous study that used data from population-based surveys and showed higher control rates in the United States compared with Canada (50% vs. 43%).[30] It is possible that participating sites from Canada were more homogenous (regional stroke centers) compared to the heterogeneity of sites seen in the United States, represented by both academic and private stroke centers. The similar baseline control rates in the United States and Latin America were unexpected, given the assumptions about the differences in healthcare access and treatment practices between Latin America and the United States. Interestingly, the mean number of antihypertensive medications was significantly different between the United States (1.9 ± 1.3) and Latin America (1.3 ± 0.9). Given the similar BP control, this could reflect differences in adherence to the antihypertensive regimen, although we do not have a measure of adherence at baseline to investigate this. Sites from the United States included the highest percentage of blacks who may have more difficult to control hypertension.[31–33]

These data highlight the challenges of managing hypertension in patients with established cerebrovascular disease.[34] The majority of patients had a history of hypertension (average duration of 10 years), were on at least 1 antihypertensive medication at study entry, and had an increasing average number of medications with higher entry SBP. Lifestyle factors including current smoking, alcohol use, and body mass index did not differ by SBP group and thus do not account for the difference in control at baseline. Comorbid risk factors were prevalent with decreasing kidney function; increasing hyperlipidemia was noted with higher levels of SBP. Information about the duration of uncontrolled hypertension prior to study entry is unavailable; however, effects on the kidneys and brain, as measured by laboratory values and MRI scans, suggest it was long-standing. These findings are consistent with adverse effects of uncontrolled

hypertension on end organs but might also reflect resistance to control conferred by end organ damage. The lower statin use in the highest SBP group, despite higher lipid values, could be viewed as a surrogate marker for less aggressive care. Examination of the follow-up data will provide information on whether the SPS3 BP protocol that included frequent follow-up, the provision of antihypertensive medications, and a focus on adherence to the treatment plan was able to achieve BP control in this challenging group.

Our data confirm results from several large studies of patients with hypertension that have reported the association between duration of diagnosed hypertension and poor control of BP.[35,36] Interestingly, the proportion of patients reporting prior symptomatic subcortical stroke/transient ischemic attack did not differ by baseline SBP. There were, however, differences in the MRI findings, with those in the highest SBP groups significantly more likely to show multiple infarcts on MRI and more severe white matter disease. Based on the disease burden noted in these patients, they would be expected to have a higher risk for recurrence of stroke and a higher risk for cardiovascular events overall. Subanalysis of the SPS3 data will need to be done to assess risk in relation to baseline BP levels and other risk factors.

The majority of patients (67%) were taking either an ACE inhibitor or an angiotensin receptor blocker at entry to the study. Although studies have provided conflicting evidence about whether ACE inhibitors and angiotensin receptor blockers reduce vascular events by mechanisms independent of BP lowering,[3,37,38] the high percentage of patients taking these medications at baseline, higher than any other class of antihypertensives, suggests that many clinicians believe in their beneficial effects beyond BP lowering. The increased use with higher SBP may also be due to the need for multiple classes of medications in these groups. Thiazide-type diuretics are recommended as initial therapy for most patients with hypertension,[11] but only about one-third of patients were taking diuretics at entry to trial. However, the most common combination of agents in those patients taking more than 1 antihypertensive medication was a diuretic and an ACE inhibitor; this practice is consistent with the secondary prevention of stroke guidelines.[28]

Although the results presented here represent community management of SBP after stroke and before entry into the trial at these 81 sites, the sample may not be fully representative of the general postlacunar stroke population as these were research trial volunteers who had to have MRI confirmation of lacunar stroke. While this may impact on the generalizability of the results, the 3,020 participants were recruited from clinical centers that were diverse in terms of urban/rural, teaching/private status, size, and country. The time between stroke and study entry was variable and, as was seen here, was associated with entry-level SBP, suggesting that there may have been less opportunity to manage SBP for those entered closer to their stroke. It is also possible that those with highest SBPs were enrolled sooner so that intensive management with the SPS3 protocol and formulary could be initiated.

In conclusion, 2.5 months after lacunar stroke, more than half of the patients had SBP exceeding the guideline-recommended upper limit, and this was particularly true for black participants. In the adjusted logistic regression model, geographic region was an independent predictor of lower entry SBP. These findings shed light on the factors associated with suboptimal control of BP in patients with recent lacunar stroke at risk for recurrence and highlight the effect of ethnic, regional, and clinical factors. Once available, data from the SPS3 study will help determine if management of BP in the setting of a protocol that focused on SBP control and with access to free medications could help minimize the disparities we observed at baseline, in particular in the patients with difficult-to-control hypertension.

REFERENCES

1. Eriksson S, Olofsson BPW. Atenolol in secondary prevention after stroke. *Cerebrovasc Dis* 1995; 5:21–26.
2. PATS Collaborating Group. Post-Stroke Antihypertensive Treatment Study: a preliminary result. *Chin Med J* 1995; 108:710–717.
3. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischemic attack. *Lancet* 2001; 358:1033–1041.
4. Gueyffier F, Boissel JP, Boutitie F, Pocock S, Coope J, Cutler J, Ekbom T, Fagard R, Friedman L, Kerlikowske K, Perry M, Prineas R, Schron E. Effect of antihypertensive treatment in patients having already suffered from stroke. Gathering the evidence. The INDANA (INdividual Data ANalysis of Antihypertensive intervention trials) Project Collaborators. *Stroke* 1997; 28:2557–2562.
5. Gueyffier F, Froment A, Gouton M. New meta-analysis of treatment trials of hypertension: improving the estimate of therapeutic benefit. *J Hum Hypertens* 1996; 10:1–8.
6. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342:145–153.
7. Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. *Stroke* 2003; 34:2741–2748.
8. Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, Davis S, Donnan G, MacMahon S, Neal B, Warlow C, Woodward M. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. *Stroke* 2004; 35:116–121.
9. Perry HM, Jr., Davis BR, Price TR, Applegate WB, Fields WS, Guralnik JM, Kuller L, Pressel S, Stamler J, Probstfield JL. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 2000; 284:465–471.
10. Chalmers J, MacMahon S, Mancia G, Whitworth J, Beilin L, Hansson L, Neal B, Rodgers A, Ni Mhurchu C, Clark T. 1999 World Health

Organization-International Society of Hypertension Guidelines for the management of hypertension. Guidelines sub-committee of the World Health Organization. *Clin Exp Hypertens* 1999; 21:1009–1060.

11. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. *JAMA* 2003; 289:2560–2571.

12. Ramsay LE, Williams B, Johnston GD, MacGregor GA, Poston L, Potter JF, Poulter NR, Russell G. British Hypertension Society guidelines for hypertension management 1999: summary. *BMJ* 1999; 319:630–635.

13. Benavente OR, White CL, Pearce L, Pergola P, Roldan A, Benavente M-F, Coffey C, McClure LA, Szychowski JM, Conwit R, Heberling PA, Howard G, Bazan C, Vidal-Pergola G, Talbert R, Hart RG. The Secondary Prevention of Small Subcortical Strokes (SPS3) study. *Int J Stroke* 2011; 6:164–175.

14. White CL, Szychowski JM, Roldan A, Benavente M-F, Pretell EJ, Del Brutto OH, Kase CS, Arauz A, Meyer BC, Meissner I, Demaerschalk BM, McClure LA, Coffey CS, Pearce LA, Conwit R, Irby LH, Peri K, Pergola PE, Hart RG, Benavente OR. Clinical features and racial/ethnic differences among the 3020 participants in the Secondary Prevention of Small Subcortical Strokes (SPS3) trial. *J Stroke Cerebrovasc Dis* [doi: 10.1016/j.jstrokecerebrovasdis.2012.03.002].

15. Pergola PE, White CL, Graves JW, Coffey CS, Tonarelli SB, Hart RG, Benavente OR. Reliability and validity of blood pressure measurement in the Secondary Prevention of Small Subcortical Strokes study. *Blood Press Monitoring* 2007; 12:1–8.

16. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjogren M, Wallin A, Ader H, Leys D, Pantoni L, Pasquier F, Erkinjuntti T, Scheltens P. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke* 2001; 32:1318–1322.

17. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J* 1965; 14:61–65.

18. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scott Med J* 1957; 2:200–215.

19. Teng EL, Hasegawa K, Homma A, Imai Y, Larson E, Graves A, Sugimoto K, Yamaguchi T, Sasaki H, Chiu D, White LR. The Cognitive Abilities Screening Instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia. *Int Psychogeriatr* 1994; 6:45–58.

20. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *JAMA* 1999; 282:1737–1744.

21. Sacco RL, Diener H-C, Yusuf S, Cotton D, Ôunpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BPL, Chen S-T, Cunha L, Dahlöf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, VanderMaelen C, Voigt T, Weber M, Yoon B-W. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008; 359:1238–51.

22. Ovbiagele B, Diener H-C, Yusuf S, Martin RH, Cotton D, Vinisko R, Donnan GA, Bath PM, Investigators P. Level of systolic blood pressure within the normal range and risk of recurrent stroke. *JAMA* 2011; 306:2137–2144.

23. Brenner DA, Zweifler RM, Gomez CR, Kissela BM, Levine D, Howard G, Coull B, Howard VJ. Awareness, treatment, and control of vascular risk factors among stroke survivors. *J Stroke Cerebrovasc Dis* 2010; 19:311–320.

24. Roumie CL, Ofner S, Ross JS, Arling G, Williams LS, Ordin DL, Bravata DM. Prevalence of inadequate blood pressure control among veterans after acute ischemic stroke hospitalization: a retrospective cohort. *Circ Cardiovasc Qual Outcomes* 2011; 4:399–407.

25. Aiyagari V, Gorelick PB. Management of blood pressure for acute and recurrent stroke. *Stroke* 2009; 40:2251–2256.

26. Jordan JD, Powers WJ. Cerebral autoregulation and acute ischemic stroke. *Am J Hypertens* 2012; 25:946–950.

27. Adams HP, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EFM. Guidelines for the early management of adults with ischemic stroke. A Guideline From the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. *Stroke* 2007; 38:1655–1711.

28. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; 42:227–276.

29. Leenen FHH, Schiffrin EL. Control rates of hypertension in North America. *Hypertension* 2010; 56:571–572.

30. Joffres MR, Hamet P, MacLean DR, L'Italien GJ, Fodor G. Distribution of blood pressure and hypertension in Canada and the United States. *Am J Hypertens* 2001; 14:1099–1105.

31. Bravata DM, Wells CK, Gulanski B, Kernan WN, Brass LM, Long J, Concato J. Racial disparities in stroke risk factors: the impact of socioeconomic status. *Stroke* 2005; 36:1507–1511.

32. Egan BM, Zhao Y, Axon RN. US Trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA* 2010; 303:2043–2050.

33. Guo F, He D, Zhang W, Walton RG. Trends in prevalence, awareness, management, and control of hypertension among United States adults, 1999 to 2010. *J Am Coll Cardiol* 2012; 60:599–606.

34. Dawes M. Why is controlling blood pressure after stroke so difficult? *CMAJ* 2013; 185:11–12.

35. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, Oliveras A, Ruilope LM. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension* 2011; 57:898–902.

36. Kim K-I, Kim Y, Kim H-J, Kang D-H, Park JB, Choi D-J, Kim C-H. Current status and characteristics of hypertension treatment by primary physicians in Korea: data from Korean Epidemiology Study on Hypertension (KEY Study). *Am J Hypertens* 2008; 21:884–889.

37. Bosch J, Yusuf S, Pogue J, Sleight P, Lonn E, Rangoonwala B, Davies R, Ostergren J, Probstfield J, evaluation HIHop. Use of ramipril in preventing stroke: double blind randomised trial. *BMJ* 2002; 324:699–702.

38. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288:2981–2997.