Clinical Features and Racial/Ethnic Differences among the 3020 Participants in the Secondary Prevention of Small Subcortical Strokes (SPS3) Trial

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This study examined the baseline characteristics, racial/ethnic differences, and geographic differences among participants in the Secondary Prevention of Small Subcortical Strokes (SPS3) study. The SPS3 trial enrolled patients who experienced a symptomatic small subcortical stroke (lacunar stroke) within the previous 6 months and an eligible lesion on detected on magnetic resonance imaging. The patients were randomized, in a factorial design, to antiplatelet therapy (aspirin 325 mg daily plus clopidogrel 75 mg daily vs aspirin 325 mg daily plus placebo) and to one of two levels of systolic blood pressure targets ("intensive" [<130 mmHg] or "usual" [130-149 mmHg]). A total of 3020 participants were recruited from 81 clinical sites in 8 countries. In this cohort, the mean age was 63 years, 63% were men, 75% had a history of hypertension, and 37% had diabetes. The racial distribution was 51% white, 30% Hispanic, and 16% black. Compared with white subjects, black subjects were younger (mean age, 58 years vs 64 years; $P < .001$) and had a higher prevalence of hypertension (87% vs 70%; $P < .001$). The prevalence of diabetes was higher in the Hispanic and black subjects compared with the white subjects (42% and 40% vs 32%; both $P < .001$). Tobacco smoking at the time of qualifying stroke was much more frequent in the Spanish participants than in subjects from North America and from Latin America (32%, 22%, and

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9%, respectively; $P < .001$). Mean systolic blood pressure at study entry was 4 mmHg lower in the Spanish subjects compared with the North American subjects ($P < .01$). The SPS3 cohort is the largest magnetic resonance imaging–defined series of patients with S3. Among the racially/ethnically diverse SPS3 participants, important differences in patient features and vascular risk factors could influence prognosis for recurrent stroke and response to interventions. **Key Words:** Lacunar—clinical trial—prevention—blood pressure—antiplatelet—cognition—small vessel disease.

Small subcortical stroke (S3), also known as lacunar stroke, is a common stroke subtype, comprising ~25% of reported ischemic strokes.[1] Although the short-term prognosis is more favorable in S3 than in other stroke subtypes, stroke recurrence ranges between 4% and 11% per year, and S3 is the most common stroke subtype associated with vascular cognitive impairment and vascular dementia.[2,3] S3s are particularly frequent in Hispanic Americans,[4,5] who may have a worse prognosis than the general population.[6]

The rationale for the Secondary Prevention of Small Subcortical Strokes (SPS3) study has been published in detail elsewhere.[7] In brief, an optimal antiplatelet strategy is lacking for secondary stroke prevention in patients with S3, due mainly to small vessel disease. The efficacy of aspirin and clopidogrel compared with aspirin alone for prevention of vascular events has been demonstrated[8-10] and has prompted evaluation in individuals with S3.

Hypertension is a highly prevalent and significant risk factor for stroke in general and particularly for S3.[11,12] Treatment of hypertension also has been associated with reduced cognitive decline.[13] Relatively little is known about the optimal target levels of blood pressure control for secondary stroke prevention in well-defined ischemic stroke subtypes, however.

The SPS3 study was designed to rigorously test in parallel whether combination antiplatelet therapy comprising aspirin plus clopidogrel is superior to aspirin alone, and whether "intensive" blood pressure lowering is superior to "usual" blood pressure management, for reducing stroke recurrence (the primary endpoint), cognitive decline, and major vascular events. A secondary aim was to compare absolute differences in the benefit of these interventions on outcomes between Hispanic and non-Hispanic white participants. We describe the demographic and clinical features of participants included in SPS3, focusing on differences according to race/ethnicity.

Methods

Design and Sample

SPS3 is a randomized, multicenter clinical trial sponsored by the National Institutes of Health, National Institute of Neurological Disorders and Stroke. Details of the study design have been published elsewhere[7]; we summarize pertinent aspects. Eligibility criteria were clinical lacunar stroke syndrome or subcortical transient ischemic attack (TIA) in the 6 months before enrollment with confirmation by magnetic resonance imaging, no clinical or radiological evidence of cortical involvement, and no surgically amenable ipsilateral carotid artery disease or major-risk cardioembolic sources. Patients with subcortical TIAs required confirmation by MRI diffusion-weighted imaging (DWI) to be eligible. Exclusion criteria included radiological or clinical evidence of a previous cortical/retinal stroke/TIA, previous intracranial hemorrhage or hemorrhagic infarct, disabling stroke, impaired renal function, high risk of bleeding, or cognitive impairment. Patients were randomized in a 2×2 factorial design to one of two interventions, antiplatelet therapy with aspirin 325 mg/day or with aspirin 325 mg/day plus clopidogrel 75 mg/day (double-blind, placebo-controlled), and to one of two target levels of systolic blood pressure control, "usual" (130-149 mmHg) or "intensive" (<130 mmHg). The SPS3 study was approved by the Institutional Review Boards of all participating centers, and all patients provided written informed consent.

Procedures

Medical history before the qualifying stroke was collected from all participants at study entry. A history of hypertension was defined by at least one of the following criteria: (1) consistent recording of hypertension in medical records for ≥1 year, (2) medical record or self-reported use of at least one antihypertensive medication and/or adjustment to achieve blood pressure control, and (3) medical record of blood pressure elevation sustained for ≥3 months. A history of diabetes was defined as chronic elevation of fasting serum glucose >120 mg/dL or chronic requirement for hypoglycemic medication. Appendix 1 provides detailed study definitions for all vascular risk factors.

Before entry, patients were screened for cognitive dysfunction with the Folstein Mini Mental Status Examination (MMSE),[14] and a detailed cognitive assessment was performed. Only patients with an MMSE score not more than 2 standard deviations below the mean for age and education were entered into the trial. All patients underwent a standardized neurologic exam,[15] and functional recovery was assessed using the modified Rankin Scale (mRS),[16,17] Barthel Index,[18] and Edinburgh Stroke Outcome Questionnaire.[19]

Classification of Race/Ethnicity

Race and ethnicity were determined primarily by self-report, using the 2 US Census 2000 questions regarding race and Hispanic/Latino ethnicity. Based on a recommended combined format, the following categories were used to collect the racial/ethnic data: American Indian or Alaskan Native; Asian or Pacific Islander; black, not of Hispanic origin; Hispanic; and white, not of Hispanic origin.[20] The first 2 categories (and "other race" category) were collapsed because of very small numbers. All participants declaring themselves as Hispanic were classified as Hispanic, including participants from Latin America. All participants declaring themselves as white (and not Hispanic) were classified as non-Hispanic white (hereinafter referred to as white). Participants from Spain were included in this category.[21] Similarly, participants self-reporting their race as black or African American (and not Hispanic) were classified as non-Hispanic black (hereinafter referred to as black). Twenty-two participants (18 from North America and 4 from Latin America) self-identified as Hispanic and black and were classified as black.

Data Analyses

Data are presented as frequency (percentage) for categorical variables and as mean (standard deviation)/median (interquartile range) for continuous variables. Our analyses examined differences by ethnic/racial subgroups. Specific comparisons were made between Hispanic and white subgroups and black and white subgroups using the χ^2 test, Student *t* test, and Wilcoxon rank-sum test as appropriate. All tests of significance were 2-sided. Significant differences at $P < .01$ and $P < .001$ are noted. Differences were also examined by geographic region. Although Mexico is part of both North America and Latin America, for comparisons made here, Mexico was included with Latin America. SAS version 9.2 (SAS Institute, Cary, NC) was used for all statistical analyses.

Results

A total of 3020 patients with a recent symptomatic S3 were recruited from 81 clinical centers in the United States, Canada, Mexico, Ecuador, Peru, Chile, Argentina, and Spain (Fig 1) between May 2003 and April 2011 and randomized into one of the 4 treatment groups. Detailed information on randomizations by clinical site is provided in Appendix 2. Average time between the qualifying stroke and study randomization was 76 ± 47 days. Demographic and clinical characteristics for the cohort overall and by race/ethnic subgroup are presented in Tables 1 and 2. In what

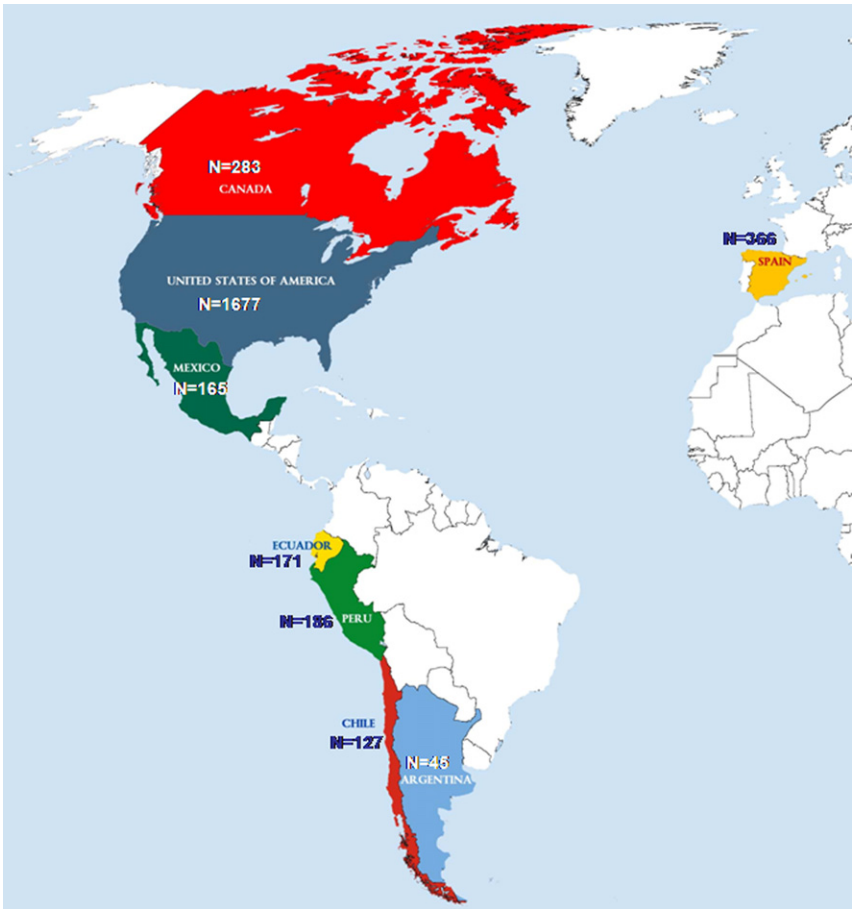

Figure 1. *Randomization by country.*

follows, we highlight findings from the overall cohort and differences by race/ethnicity.

SPS3 Cohort

The mean patient age was 63 ± 11 years, and 63% of the cohort was male (Table 1). The most prevalent risk factors were hypertension (75%), hyperlipidemia (49%), and diabetes (37%). Thirty percent reported a parental history of stroke, 10% reported a previous stroke, and 5% reported a TIA. Approximately one-third of the patients reported taking an antithrombotic medication regularly in the 7 days before the qualifying event, with 28% reporting aspirin specifically.

In the vast majority of patients (97%), the qualifying event was a stroke, with pure motor hemiparesis the most common presenting syndrome (33%), followed by sensorimotor stroke (31%). Only 6% of the cohort presented with a dysarthria clumsy-hand syndrome. Site investigators determined the localization of lesions based on clinical and radiological data; they localized 24% of lesions to the corona radiata/centrum semiovale, 28% to the basal ganglia/internal capsule, 22% to the thalamus and 26% to the brainstem or cerebellum (data not shown).

Table 2 provides information on selected clinical characteristics at the time of trial entry (approximately 2.5 months after stroke). Two-thirds of the overall cohort demonstrated good functional recovery from the

Table 1. *Demographic and clinical characteristics of study participants*

	Overall (n = 3020)	Non-Hispanic white (n = 1538)	Hispanic (n = 916)	Non-Hispanic black (n = 492)*
Mean age, years	63 ± 11	64 ± 10.8	64 ± 10.7	58 ± 9.5†
Male, %	63	65	63	54†
Lifestyle behaviors before qualifying stroke				
Smoking status, %			†	‡
Never	40	35	50	32
Former	40	42	40	37
Current	20	23	10	31
Alcohol use (≥7 drinks per week), %	13	17	9†	9†
Exercise, times per week, mean ± SD	3.1 ± 3	4 ± 3	2 ± 2.8†	2 ± 2.7†
Medical history before qualifying event, %				
Hypertension	75	70	76†	87†
Hyperlipidemia	49	52	38†	58
Diabetes	37	32	42†	40†
Parental history of stroke	30	31	25†	33
Ischemic heart disease	11	13	6†	12
Previous symptomatic small subcortical stroke	10	9	12	13‡
Previous subcortical TIA	5	6	4	5
Intermittent claudication/peripheral vascular disease	3	4	1†	4
Heart failure	0	0	0	1
Antithrombotic medication used regularly in 7 days before qualifying event, %	31	37	22†	32
Aspirin used regularly in 7 days before qualifying event, %	28	33	21†	26‡
Qualifying event, %				
Subcortical stroke	97	96	98	98
Subcortical TIA with DWI-positive corresponding lesion	3	4	2	2
Clinical syndrome of qualifying event, %			†	‡
Pure motor hemiparesis	33	30	40	31
Sensorimotor stroke	31	29	33	34
Pure sensory stroke	10	12	7	10
Ataxic hemiparesis	9	11	5	13
Dysarthria clumsy-hand syndrome	6	8	3	5
Other	11	11	12	6

*Includes 22 patients who also reported Hispanic ethnicity.
†Significantly different from the non-Hispanic white population at $P \leq .001$.
‡Significantly different from the non-Hispanic white population at $P \leq .01$.

Table 2. *Selected clinical characteristics measured at trial entry*

	Overall (n = 3020)	Non-Hispanic white (n = 1538)	Hispanic (n = 916)	Non-Hispanic black (n = 492)*
Functional recovery, %†				
Barthel Index ≥95	80	86	68‡	83
mRS score of 0-1	67	71	65‡	55‡
BMI, mean ± SD	29.1 ± 6.8	29 ± 5.8	28 ± 5.7§	31 ± 10.6‡
Systolic blood pressure, mmHg, mean ± SD	143 ± 19	141 ± 17.2	144 ± 20‡	147 ± 19.9‡
Diastolic blood pressure, mmHg, mean ± SD	78 ± 11	77 ± 9.9	79 ± 11‡	82 ± 11.6‡
Medications at time of trial entry, %				
Antihypertensive	85	83	84	92‡
Angiotensin-converting enzyme inhibitor	52	49	55§	58‡
Diuretic	36	36	26‡	56‡
Calcium channel blocker	26	23	24	38‡
Beta blocker	25	25	17‡	37‡
Angiotensin receptor blocker	16	17	18	9‡
Lipid-lowering medication	73	76	65‡	76
Statin	69	72	61‡	72
Hypoglycemic medication	33	28	39‡	37‡
Selected laboratory values, mean ± SD				
Glucose, mg/dL	125 ± 55.1	124 ± 50.3	125 ± 59.2	130 ± 61.2
Glycosylated hemoglobin, % (diabetics only)	8.3 ± 2.2	7.7 ± 2.2	8.6 ± 2.1‡	9.1 ± 2.3‡
Total cholesterol, mg/dL	187 ± 49.9	187 ± 49.2	183 ± 48.8	196 ± 53.0‡
Low-density lipoprotein cholesterol, mg/dL	108 ± 45.7	106 ± 47.4	105 ± 42.8	120 ± 43.4‡
High-density lipoprotein cholesterol, mg/dL	45 ± 21.3	46 ± 24.8	43 ± 15.8‡	47 ± 18.2
Triglycerides, mg/dL	164 ± 119.2	162 ± 120.2	180 ± 129.5‡	139 ± 84.3‡

*Includes 22 patients who also reported Hispanic ethnicity.

†Barthel Index ranges from 0 to 100, with higher scores indicating better function; mRS score ranges from 0 to 6, with lower scores indicating better function.

‡Significantly different from the non-Hispanic white population at $P \leq .001$.

§Significantly different from the non-Hispanic white population at $P \leq .01$.

qualifying stroke at study enrollment, as indicated by a mRS score of 0 or 1. Of note, the mean body mass index (BMI) was 29 ± 6.8 kg/m^2, very close to the accepted diagnostic criterion for obesity of 30 kg/m^2. The mean systolic and diastolic blood pressures at baseline were 143 ± 19 mmHg and 78 ± 11 mmHg, respectively. A high percentage of patients reported taking antihypertensive medications (85%) and lipid-lowering medications (73%) at trial entry. Of note, mean serum glucose level was elevated in the overall cohort (125 ± 55.1 mg/dL), and mean glycosylated hemoglobin was elevated in the subgroup of patients with diabetes (8.3% ± 2.2%).

Racial/Ethnic Comparisons

The cohort was 51% non-Hispanic white, 30% Hispanic, and 16% non-Hispanic black (Fig 2). Seventy-four participants (3%) self-reported race as American Indian/Alaskan Native, Asian/Pacific Islander or "other." Because of the small numbers and heterogeneity of the "other" group, data for these patients are not presented.

The average age of black participants at trial entry was 58 years, significantly younger than the average age of 64 years for both Hispanic and white participants (both $P < .001$) (Table 1). There were significant differences by race/ethnicity in lifestyle behaviors, including smoking status, alcohol use, and regular exercise. Compared with whites, both Hispanic and black participants were significantly more likely to have a history (before the qualifying stroke) of hypertension (70% vs 76% and 87%, respectively; both $P < .001$) and diabetes (32% vs 42% and 40%, respectively; both $P < .001$). In contrast, whites were significantly more likely than Hispanics to have a history of ischemic heart disease (13% vs 6%; $P < .001$). Blacks were significantly more likely than whites to report a previous symptomatic S3 (13% vs 9%; $P < .01$), but significantly less likely to report regular aspirin in the 7 days before the qualifying event (26% vs 33%; $P < .01$). Hispanics also were also less likely than whites to report regular aspirin use (21% vs 33%; $P < .001$).

An mRS score of 0-1 was recorded at study enrollment for 71% of white participants (Table 2). In contrast, this same level of recovery was demonstrated by only 65% of Hispanic participants and by only 55% of black participants (both $P < .001$). Compared with whites (141 ± 17.2 mm Hg), average systolic blood pressure was significantly higher in Hispanics and blacks (144 ± 20 mm Hg and 147 ± 19.9 mm Hg, respectively; both $P < .001$). Blacks

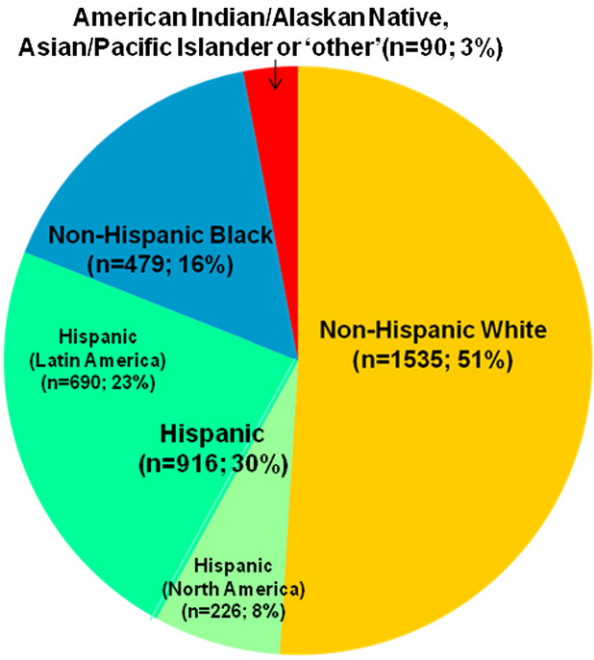

Figure 2. *Racial/ethnic distribution.*

were more likely than whites to be using antihypertensive medication at study entry (92% vs 83%; $P < .001$), and racial/ethnic differences were seen by antihypertensive medication class. Hispanics were less likely than whites to be taking lipid-lowering medications at study entry (65% vs 76%; $P < .001$). Mean glycosylated hemoglobin was higher in whites than in both Hispanics and blacks (7.7% ± 2.28.6% ± 2.1 and 9.1% ± 2.3 respectively; both $P < .001$).

Geographic Comparisons

Of the 3020 participants in SPS3, 65% were from North America (United States and Canada), 23% were from Latin America (Mexico, Ecuador, Peru, Chile, and Argentina), and 12% were from Spain (Table 3). Although the majority of Hispanic participants were from Latin American sites, participants from North America showed diversity, with 40% of participants classified as race/ethnicity other than non-Hispanic white. Participants from North America were significantly younger at stroke onset compared with those from Latin America and Spain (mean age, 62 vs 66 and 65 years, respectively; $P < .01$) and less likely to be male (male preponderance, 60% vs 65% and 75%, respectively; $P < .01$). Tobacco smoking at the time of qualifying stroke was much more frequent among Spanish participants than among North American and Latin American participants (32% vs 22% and 9%, respectively; $P < .01$). There were significant differences in vascular risk factors by geographic region. Participants from Spain were significantly less likely to report a history of hypertension compared with those from North America and Latin America (60% vs 78% and 76%, respectively; $P < .01$) and entry systolic blood pressure was 4 mmHg lower in Spanish participants compared with North American participants ($P < .01$). Participants from North America were significantly more likely than those fron Latin American and Spain to report a history of hyperlipidemia and ischemic heart disease ($P < .01$). Participants from North America were significantly more likely than those from Latin America and Spain to report regular aspirin use in the 7 days before the qualifying stroke (37% vs 20% and 21%, respectively; $P < .01$). There were significant differences by geographic region in the use of both antihypertensive and lipid-lowering medications at trial entry ($P < .01$). There also were significant differences in mean BMI by geographic region, with the highest mean BMI found in North America (30 ± 7.5), followed by Spain (28 ± 4) and then Latin America (27 ± 5).

Discussion

Our analysis of this large, racially and geographically diverse cohort of patients with recent subcortical ischemic stroke has identified significant differences in age, sex, and vascular risk factors among the white, black, and Hispanics participants. These differences are likely to impact the prognosis for recurrent stroke and cognitive impairment and perhaps the response to blood pressure control and antiplatelet therapies. For example, blood pressure control may offer a greater relative benefit to blacks (who have the highest prevalence of hypertension) compared with Hispanics (who have the highest prevalence of diabetes). These hypotheses will be addressed using outcome data involving stroke, cognition and death accumulated during the anticipated 4-year mean follow-up of this cohort.

The differences in stroke risk factors among the white, black, and Hispanic participants reported here are consistent with findings from previous studies and may reflect racial/ethnic-based disparities in stroke care.[21] Of particular note is the 6-year difference in age of onset of stroke, with an average age of 58 ± 9.5 years for black participants, compared with 64 ± 10.8 years for whites and 64 ± 10.7 years for Hispanics. This younger age, coupled with the level of functional recovery at entry to trial, with only 55% of blacks reporting normal or near-normal status compared with 65% for Hispanics and 71% for whites, underscores the important effect of stroke for blacks on disability-free years. Furthermore, the black participants were more likely to have a history of previous subcortical stroke, but yet less likely to report regular aspirin use in the 7 days before the index stroke. Hispanic participants were similarly less likely to report regular use of antiplatelet medication before the index stroke. Morgenstern et al[22] reported that only two-thirds of Mexican American participants in the Brain Attack Surveillance in Corpus Christi (BASIC) project were taking antiplatelet medication for secondary stroke prevention.

Table 3. *Selected demographic and clinical characteristics stratified by geographic region*

	North America* (n = 1960)	Latin America* (n = 694)	Spain (n = 366)
Race/ethnicity, n (%)†			
Non-Hispanic white	1172 (59.8)	0	366 (100)
Hispanic	226 (11.5)	690 (99.4)	0
Non-Hispanic black‡	488 (24.9)	4 (0.6)	0
Other§	74 (3.8)	0	0
Age, years, mean ± SD†	62 ± 11	66 ± 11	65 ± 11
Male, %†	60	65	75
Lifestyle behaviors before qualifying stroke			
Smoking status, %†			
Never	36	52	33
Former	42	38	35
Current	22	9	32
Alcohol use (≥ 7 drinks per week), %†	13	8	22
Exercise, times per week, mean ± SD†	3 ± 3	2 ± 3	5 ± 3
Medical history before qualifying stroke, %			
Hypertension†	78	76	60
Hyperlipidemia†	57	33	37
Diabetes	36	38	36
Parental history of stroke†	32	23	28
Ischemic heart disease†	14	4	5
Previous symptomatic small subcortical stroke	10	11	8
Previous subcortical TIA	6	4	6
Intermittent claudication/peripheral vascular disease†	4	1	5
Heart failure	1	0	0
Antithrombotic medication used regularly in 7 days before qualifying stroke, %†	37	20	21
mRS score 0-1, %	67	64	67
Barthel Index ≥95, %†	85	64	84
BMI, mean ± SD†	30 ± 7.5	27 ± 5	28 ± 4
Systolic blood pressure, mmHg, mean ± SD†	143 ± 19	144 ± 21	139 ± 16
Diastolic blood pressure, mmHg, mean ± SD	78 ± 11	79 ± 12	78 ± 9
Antihypertensive medications, %†	87	84	75
Lipid-lowering medications, %†	77	62	72
Hypoglycemic medications, %	33	34	34

*North America includes United States and Canada; Latin America includes Mexico, Ecuador, Peru, Chile, and Argentina.
†Difference among groups significant at $P < .01$.
‡Includes 22 patients (18 in North America and 4 in Latin America) who also reported Hispanic ethnicity.
§Includes those who reported their race as American Indian/Alaskan Native, Asian/Pacific Islander, or other.

Consistent with previous reports, black participants were significantly more likely to be hypertensive, with a higher mean blood pressure at trial entry.[23-25] Similar to findings from the BASIC project,[26] Hispanics had a significantly higher prevalence of diabetes compared with whites (42% vs 32%), whereas whites had a significantly higher prevalence of ischemic heart disease compared with Hispanics (13% vs 6%). The lower prevalence of diabetes in Latin American participants compared with Hispanic participants overall (38% vs 42%) suggests that the higher rate of diabetes in Hispanics may be driven by a high prevalence in North American Hispanics.

SPS3 was designed to address several important clinical and scientific questions relevant to a common stroke subtype, lacunar infarct. The inclusion criteria were stringent to ensure that small-vessel disease was the most likely underlying mechanism of the lacunar infarct. The exclusion criteria were carefully considered to enhance the generalizability of the trial findings to the millions of patients with this common vascular disorder. Nonetheless, clinical trials suffer from problems with external validity, and SPS3 is no exception. To examine whether the SPS3 sample is representative of the larger population of patients with lacunar stroke, we compared baseline characteristics from SPS3 participants with available characteristics from published series of both hospital and population-based patients with lacunar stroke, selected because patients in the series underwent neuroimaging (Table 4). These samples are diverse in terms of country of origin as well as study period, with publications dating between 1989 and 2011.

Table 4. *Lacunar stroke series*

Study	Country	Sample size	Mean age, years	Male, %	Imaging, %		Vascular risk factors, %						
					CT	MRI	HTN	DM	IHD	PVD	TIA	Stroke	HPL
Norrving and Cronqvist[31]	Sweden	61	58	67	100		53	8	8	NR	NR	NR	16
Tegeler et al[32]	US	55	61 ± 10	71	100		60	35	NR	NR	7	24	NR
Landi et al[33]	Italy	88	66 ± 12	63	100		65	19	11	NR	23	NR	NR
Toni et al[34]	Italy	170	67 ± 10	65	100		56	16	22	NR	23	NR	NR
Salgado et al[35]	Portugal	145	65 ± 11	64	100		72	25	5	8	18	NR	28
Yip et al[36]	Taiwan	195	66 ± 9	54	100		85	36	14	NR	NR	24	18
Marti-Vilalta and Arboix[37]	Spain	399	67 ± 11	NR	100		76	28	22	10	9	NR	12
Awada and Al Rajeh[38]	Saudi Arabia	248	59	68	100		57	56	14	NR	NR	NR	NR
Hajat et al[39]	UK	282	72	48	NR		66	21	26	NR	NR	20	NR
Yokota et al[40]	Japan	556	66 ± 11	70	100		75	27	9	NR	15	NR	32
Soda et al[41]	Japan	198	70 ± 10	66	100		69	37	NR	NR		24	39
Wessels et al[30]	Germany	63	63	57		100	88	30	NR	NR	NR	30	38
Bejot et al[42]	France	89	74	42	100		73	19	NR	NR	11	NR	61
Turin et al[43]	Japan	751	70 ± 0.7	55	100		57	21	NR	NR	6	NR	19
Wardlaw et al[44]	UK	67	64.5	75		100	52	NR	12	3	8	3	NR
Melkas et al[29]	Finland	63	73 ± 7	50	100		41	24	32	16	NR	14	NR
SPS3[7]	North America, Latin America, Spain	3020	63 ± 11	63		100*	75	37	7	3	5	10	49

Abbreviations: DM, diabetes mellitus; HPL, hyperlipidemia; HTN, hypertension; IHD, ischemic heart disease; NR, not reported; PVD, peripheral vascular disease.
Data are presented as mean ± SD or percentage.
*Six patients (0.1%) were unable to undergo MRI related to medical reasons and were entered into the study with CT scan that demonstrated the corresponding lesion.

The average age at trial entry for SPS3 participants was 63 years, falling within the range seen in the present series and consistent with reports of a younger average age of persons with lacunar stroke compared with those with other stroke subtypes.[27,28] There is considerable variability in the prevalence of vascular risk factors across the reported series. For example, the prevalence of hypertension ranges from a low of 41% in the Finnish cohort[29] to a high of 88% in the German cohort,[30] with the majority of studies reporting at least 60% prevalence and SPS3 reporting 75%. SPS3 is among the studies reporting the highest prevalence of diabetes. Differences in prevalence may be related to inconsistencies in how the vascular risk factors were defined, as well as in the sources of participants. SPS3 is the only clinical trial of these series. Despite the strict criteria imposed on patient inclusion in a clinical trial, the baseline characteristics of the SPS3 cohort fall within the ranges reported in these series, which suggests that the data from SPS3 are applicable to the overall population of patients with lacunar stroke.

The lack of generally accepted and consistently applied definitions of ethnicity across studies[21] posed a challenge in the present study, particularly with the inclusion of sites from Spain and Latin America. We made several assumptions in our classification scheme, including that the participants from South America were Hispanic and that the participants from Spain were not Hispanic. Even within each racial/ethnic group, there is considerable heterogeneity relative to culture and environment, which limits conclusions regarding any differences between racial/ethnic groups. Furthermore, our results highlighting racial/ethnic differences are presented for the purpose of fully describing the clinical features of the SPS3 cohort; because our data are unadjusted and cross-sectional, we are unable to draw conclusions regarding the reasons for differences by race/ethnicity. These unadjusted findings do emphasize the greater prevalence of stroke risk factors in blacks and Hispanics, as well as the greater impact on functional recovery at approximately 3 months after the index stroke.

In conclusion, our comparison of baseline characteristics in the SPS3 cohort and other published lacunar stroke series demonstrates that the SPS3 cohort is representative of patients with lacunar stroke in general. This finding supports the generalizability of the SPS3 trial results to the millions of patients around the world with this common disorder. In light of its multiracial cohort, the SPS3 results should further the understanding of racial/ethnic differences in stroke risk and prevention.

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Appendix 1. *Operational Definitions of Vascular Risk Factors*

Hypertension	Present if any of the following criteria was met: • Consistent recording of hypertension in medical records for ≥1 year • Medical record or self-report of use of at least one antihypertensive medication and/or adjustment to achieve blood pressure control • Recording in medical records of elevation of blood pressure sustained for ≥3 months
Diabetes	Present if either of the following criteria was met: • Chronic elevation of the fasting serum glucose exceeding 120 mg/dL • Chronic requirement for hypoglycemic medications • Report of antihypoglycemic medication use within 3 months of study entry
Ischemic heart disease	Includes history of definite myocardial infarction, definite/atypical angina, or revascularization procedure. Myocardial infarction definite if any of the following criteria was met: • Medical records are available to document serial ECG/enzyme changes compatible with myocardial infarction • History of compatible clinical syndrome of prolonged chest pain plus either abnormal Q waves in appropriate ECG leads or diminishing R-wave amplitude in 2 or more adjacent precordial leads, or segmental left ventricular wall motion abnormality • Angiographic evidence of coronary occlusive disease with associated ventricular dyssynergy. • Angina, defined as discomfort occurring anywhere in the anterior chest, back, jaw, neck or shoulder, requiring rest or nitroglycerin for relief; and/or written medical record documenting history of angina by clinical symptoms and cardiac antianginal drug therapy, and/or history of invasive cardiac procedure for the treatment of anginal symptoms (ie, percutaneous transluminal coronary angioplasty or coronary artery bypass graft)

Heart failure	Diagnosis based on a clinically convincing situation (complete medical record documentation if not currently active), which could include constellations of: • Orthopnea, dyspnea on exertion, and edema responding dramatically to diuretics • S3 gallop and pulmonary rales • Chest X-ray evidence of cardiomegaly/vascular redistribution • Elevated left ventricular filling pressure or pulmonary wedge pressure at catheterization
Peripheral vascular disease	Present if either of the following criteria was met: • Exertional pain, cramping or burning, usually in the lower legs • Arteriographic or sonographic evidence of peripheral vascular disease
Hyperlipidemia	Current treatment with a lipid-lowering drug or laboratory data confirming fasting hyperlipidemia

Appendix 2. Countries and Clinical Sites (Number of Enrolled Patients)

United States, 50 sites (n = 1677): University of Texas Health Science Center at San Antonio, San Antonio, TX (108); Boston University, Boston, MA (92); Mayo Clinic Rochester, Rochester, MN (90); University of California San Diego, San Diego, CA (82); Mayo Clinic, Scottsdale, AZ (74); Metro Health System, Cleveland, OH (70); Minneapolis Medical Research Foundation, Minneapolis, MN (68); University of Kentucky Medical Center, Lexington, KY (64); St Louis University, St Louis, MO (57); Wayne State University School of Medicine, Detroit, MI (57); Methodist Hospital, Houston, TX (57); University of Arizona, Tucson, AZ (54); St John's Mercy Medical Center, St Louis, MO (52); Henry Ford Hospital, Detroit, MI (51); Melbourne Internal Medical Associates, Melbourne, FL (50); Vanderbilt University Medical Center, Nashville, TN (46); Columbia University Medical Center, New York, NY (45); Ohio State University Medical Center, Columbus, OH (41); University of South Alabama, Mobile, AL (39); Rochester General Hospital, Rochester, NY (34); University of Texas Southwestern, Dallas, TX (33); Medical College of Wisconsin, Milwaukee, WI (33); University of Rochester Medical Center, Rochester, NY (32); Oregon Health and Science University, Portland, OR (30); Wake Forest University School of Medicine, Winston-Salem, NC (29); University of Washington, Seattle, WA (27); Cooper Health System, Camden, NJ (26); St Joseph's Hospital and Medical Center, Phoenix, AZ (25); Marshfield Clinic Research Foundation, Marshfield, WI (24); Sutter Medical Center Sacramento, Sacramento, CA (22); Iowa Neurology Research, Inc, Des Moines, IA (21); University of Miami Miller School of Medicine, Miami, FL (17); Johns Hopkins Bayview Medical Center, Baltimore, MD (16); Case Western Reserve University, Cleveland, OH (16); Helen Hayes Hospital, Rensselaer, NY (15); Emory University, Atlanta, GA (13); Research Foundation of SUNY Buffalo, Buffalo, NY (9); Cedars Sinai Medical Center, Los Angeles, CA (9); Florida Neurovascular Institute, Tampa, FL (9); North General Hospital, New York, NY (9); Mt Sinai School of Medicine, New York, NY (9); Washington University School of Medicine at St Louis, MO (5); Regents of the University of California, Fresno, CA (4); Loyola University of Chicago, Chicago, IL (4); Indiana University, Indianapolis, IN (2); University of Illinois at Chicago, Chicago, IL (2); Colorado Neurological Institute, Englewood, CO (2); Spartanburg Regional Medical Center, Spartanburg, SC (1); Sunrise Hospital and Medical Center, Las Vegas, NV (1); Stanford University, Stanford, CA (1)

Canada, 8 sites (n = 283): Centre Hospitalier affilié Universitaire de Québec, QC (48); Montreal General Hospital, McGill University, Montreal, QC (42); Capital District Health Authority, Halifax, NS (41); The Ottawa Hospital, Ottawa, ON (37); Jewish General Hospital, McGill University, Montreal, QC (37); Centre de Recherche, Greenfield Park, QC (36); University of Calgary, Calgary, AB (35); University of Alberta, Edmonton, AB (7)

Ecuador, 1 site (n = 171): Hospital Clínica Kennedy, Guayaquil

Chile, 2 sites (n = 127): Hospital Naval Almirante Nef, Viña del Mar (69); Hospital Clínico Universidad Católica de Chile, Santiago (58)

Mexico, 4 sites (n = 165): Instituto Nacional de Neurología y Neurocirugía, México DF (92); Hospital Civil de Guadalajara, Jalisco (31); Instituto Nacional de Ciencias Médicas y Nutrición, México DF (26); Hospital de la Universidad Autónoma de Nuevo León, Monterrey, Nuevo León (16)

Argentina, 5 sites (n = 45): Centro Neurológico, Buenos Aires (14); Hospital Británico, Buenos Aires (12); Hospital Ramos Mejía, Buenos Aires (7); Instituto FLENI, Buenos Aires (8); Hospital Universitario Austral, Buenos Aires (4)

Peru, 1 site (n =186): Fundación Cayetano Heredia, Lima

Spain, 10 sites (n = 366): Hospital Universitario de Bellvitge, Barcelona (66); Hospital del Mar, Barcelona (58); Hospital Universitario Sagrat Cor, Barcelona (54); Corporació Sanitaria Parc Taulí, Sabadell (51); Hospital Universtario Dr Josep Trueta, Girona (45); Hospital Universitario German Trias i Pujol, Badalona (27); Hospital de la Santa Creu i Sant Pau, Barcelona (25); Hospital Universitario de Santiago de Compostela (23); Hospital La Paz, Madrid (15); Hospital General de Cataluña, Barcelona (2)