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

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Abstract

AIM—To describe the baseline characteristics, racial/ethnic differences, and geographic differences among participants in the Secondary Prevention of Small Subcortical Strokes (SPS3) study.

METHODS—The SPS3 trial enrolled patients with a symptomatic small subcortical stroke (lacunar stroke) within the prior 6 months and an eligible lesion on MRI, who 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) vs. "usual" (130–149 mmHg)).

RESULTS—Among the 3020 participants recruited from 81 clinical sites in 8 countries, the mean age was 63 years, 63% were men, 75% had a history of hypertension, and 37% were diabetic. Fifty-one percent were White, 30% Hispanic, and 16% Black. Black participants were younger (mean age 58 years vs. 64 years, p<0.001) and more often had hypertension (95% vs. 89%, p<0.001) than White participants. Hispanic and Black participants more often had diabetes than White participants (42%, 40% vs. 32% respectively, both p<0.001). Tobacco smoking at the time of qualifying stroke was much more frequent among Spanish participants (32%) than those from North America (22%) or Latin America (8%) (p<0.001); systolic blood pressure at study entry was 5 mmHg lower among Spanish vs. North American participants (p<0.01).

CONCLUSIONS—The SPS3 cohort is the largest MRI-defined series of patients with S3. Among the racially/ethnically diverse SPS3 participants, there are important differences in patient features and vascular risk factors could influence prognosis for recurrent stroke and response to interventions.

Clinical Trial Registration Information—The SPS3 study is registered on www.clinicaltrials.gov (NCT00059306).

BACKGROUND

Small subcortical strokes (S3), also known as lacunar strokes, are a common stroke subtype, comprising about 25% of ischemic strokes.[1] While short-term prognosis is more favorable than in other stroke sub-types, 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] S3 are particularly frequent in Hispanic Americans,[4–5] who may have a worse prognosis.[6]

The rationale for the Secondary Prevention of Small Subcortical Strokes (SPS3) study has been published in detail elsewhere.[7] In brief, the optimal antiplatelet strategy is lacking for secondary stroke prevention in patients with S3, most due 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 prompted evaluation in those specifically with S3.

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

The SPS3 study was designed to rigorously test in parallel whether combination antiplatelet therapy consisting of 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 benefit of these

interventions on outcomes between Hispanic and non-Hispanic White participants. In this report, the demographic and clinical features of participants included in SPS3 are described, focusing on differences according to race/ethnicity.

METHODS

Design and Sample

SPS3 is a randomized, multicenter clinical trial, sponsored by the U.S. NINDS/NIH. Details of the study design have been published elsewhere with pertinent aspects summarized here. [7] Patients were eligible if they had a clinical lacunar stroke syndrome or subcortical transient ischemic attack (TIA) in the 6 months prior to enrollment with MRI confirmation, were without clinical and radiological evidence of cortical involvement, and without surgically-amenable ipsilateral carotid artery disease and major-risk cardioembolic sources. Subcortical TIAs required positive MRI diffusion imaging to be eligible. Exclusion criteria included radiological or clinical evidence of a prior 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-by-2 factorial design, to two interventions: (i) antiplatelet therapy: aspirin (325 mg/day) vs. aspirin (325 mg/day) plus clopidogrel (75 mg/day) (double blind, placebo control); and (ii) two target levels of systolic blood pressure control, "usual" (130–149 mmHg) vs. "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 prior to 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: i) consistent recording of hypertension in medical records   1 year; ii) medical record or self-report of use of at least one antihypertensive medication and/or adjustment to achieve blood pressure control; iii) recording in medical records of elevation of blood pressure sustained 3 months. A history of diabetes was defined as chronic elevation of the fasting serum glucose exceeding 120 mg/dl or chronic requirement for hypoglycemic medications. Appendix 1 provides detailed study definitions for all vascular risk factors.

Prior to entry, patients were screened for cognitive dysfunction with the Folstein Mini Mental Status Examination (MMSE),[14] and a detailed cognitive assessment was performed. Patients were entered into the trial only if their MMSE did not fall more than two standard deviations below the mean for age and education. All patients underwent a standardized neurological exam,[15] functional recovery was assessed using the modified Rankin Scale,[16–17] Barthel Index,[18] and Edinburgh Stroke Outcome Questions.[19]

Classification of Race/Ethnicity

Race and ethnicity were determined primarily by self-report, using the two Census 2000 questions regarding race and Hispanic/Latino ethnicity. Based on a recommended combined format, the following categories were utilized 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 two categories (and 'other race' category) were collapsed due to 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 (hereafter 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 (hereafter referred to as Black). There were

22 participants (18 from North America and 4 from Latin America) who self-identified as Hispanic and Black and these were classified as Black.

Data Analyses

Frequencies (percentages), means (standard deviations) / medians (interquartile ranges) are presented for categorical and continuous variables, respectively. Analyses examined differences by ethnic/racial sub-groups. Specific comparisons were made between Hispanic and White sub-groups and Black and White sub-groups using Chi-square tests, Student t-tests, and Wilcoxon rank sum tests as appropriate. All tests of significance were 2-sided. Significant differences at the 0.01 and 0.001 levels of significance are noted. Differences were also examined by geographic region. Although Mexico is part of both North America and Latin America, for comparisons undertaken here, Mexico was included with Latin America. SAS version 9.2 (SAS Institute Inc, Cary, NC) was used for all statistical analyses.

RESULTS

A total of 3020 patients with a recent symptomatic S3, from 81 clinical centers in USA, Canada, Mexico, Ecuador, Peru, Chile, Argentina, and Spain (Figure 1), were recruited between May 2003 and April 2011 and randomized into one of the four treatment groups. Detailed information on randomizations by clinical site can be found in Appendix 2. Average time between qualifying stroke and randomization was 76 ± 47 days. Demographic and clinical characteristics for the overall cohort and by race/ethnic subgroup are presented in Tables 1 and 2, with findings from the overall cohort and differences by race/ethnicity highlighted in the text below.

SPS3 Cohort

The mean 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% a prior stroke, and 5% a TIA. About one-third of the cohort reported taking antithrombotic medication regularly in the 7 days prior to the qualifying event, with 28% reporting aspirin specifically.

The qualifying event for almost all participants was a stroke (97%), with pure motor hemiparesis the most common presenting syndrome (33%), followed by sensorimotor strokes (31%), with only 6% of the cohort presenting with a dysarthria clumsy-hand syndrome. Site investigators determined the localization 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 their stroke). Two-thirds of the overall sample showed good functional recovery from the qualifying stroke at study enrollment, as indicated by a modified Rankin Scale score of 0 or 1. It is noteworthy that the mean body mass index (BMI) was 29 ($\pm$ 6.8), very close to the accepted diagnostic criterion of obesity (30 kg/m^2). The mean systolic and diastolic blood pressures of the participants at baseline were 143 ± 19 mmHg and 78 ± 11 mmHg, respectively. A high percentage of patients reported taking anti-hypertensive medications (85%) and lipid-lowering medications (73%) at trial entry. Of note, glucose was elevated in the overall cohort (125 mg/dl $\pm$ 55.1) and glycosylated hemoglobin was elevated in the sub-group of diabetics (8.3% $\pm$ 2.2).

Racial/Ethnic Comparisons

Fifty-one percent of the sample was classified as non-Hispanic White, 30% as Hispanic, and 16% as Non-Hispanic Black (Figure 2). There were 74 participants (3%) who reported their race as American Indian/Alaskan Native, Asian/Pacific Islander or 'other'. Because of the small numbers and heterogeneity of the 'other' group, these data are not presented.

The average age of Black participants at trial entry was 58 years, significantly younger compared with the average age of 64 years for both Hispanic and White participants (both p<0.001) (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 (prior to the qualifying stroke) of hypertension (70% vs. 76% and 87% respectively; both p< 0.001) and diabetes (32% vs. 42% and 40% respectively; both p<0.001). In contrast, Whites were significantly more likely to have a history of ischemic heart disease compared with Hispanics (13% vs. 6%; p<0.001). Black participants were significantly more likely to report a prior symptomatic S3 compared with Whites (13% vs. 9%, p<0.01) but significantly less likely to report regular aspirin in the 7 days prior to the qualifying event compared with White participants (26% vs. 33%; p<0.01). Hispanic participants were also less likely to report regular aspirin use compared with Whites (21% vs. 33%; p<0.001).

Seventy-one percent of White participants scored 0 to 1 on the modified Rankin Scale at study enrollment (Table 2). In contrast, this same level of recovery was shown by only 65% of Hispanic and 55% of Black participants (both p<0.001). Compared with White participants (141 ± 17.2 mm Hg), average systolic blood pressure was significantly higher among Hispanic and Black participants (144 ± 20 mm Hg and 147 ± 19.9 mm Hg respectively; both p<0.001). Black participants were more likely to be using anti-hypertensive medications (92%) compared with White participants (83%) (p<0.001) at study entry and there were racial/ethnic differences by anti-hypertensive class. Hispanic participants were less likely to be taking lipid-lowering medications (65%) at study entry compared with White participants (76%) (p<0.001). Compared with Whites (7.7% ± 2.2), glycosylated hemoglobin was even higher for Hispanic and Black participants (8.6% ± 2.1 and 9.1% ± 2.3 respectively; both p<0.001).

Geographic Comparisons

Of the 3020 participants in SPS3, 65% were from North America (United States and Canada), 23% from Latin America (Mexico, Ecuador, Peru, Chile, and Argentina), and 12% 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 than those from Latin America and Spain (62, 66, and 65 years respectively; p <0.01) and less likely to be male (60%, 65%, 75% respectively; p <0.01). Tobacco smoking at the time of qualifying stroke was much more frequent among Spanish participants (32%) than among those from North American (22%) or Latin American (8%) sites (p<0.01). 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 to North and Latin America (60%, 78%, 76% respectively; p <0.01) and entry systolic blood pressure was 5 mmHg lower among Spanish vs. North American participants (p<0.01). Participants from North America were significantly more likely to report a history of hyperlipidemia and ischemic heart disease compared with participants from Latin America and Spain (p< 0.01). Participants from North America were significantly more likely to report regular aspirin use in the 7 days before the qualifying stroke (37%) compared with participants from Latin America (20%) and Spain (21%)

(p<0.01). There were also significant differences by geographic region in the use of both antihypertensive and lipid-lowering medications at trial entry (p<0.01). There were significant differences in mean body mass index (BMI) by geographic region, with the highest mean BMI found in North America (30 ± 7.5), followed by Spain (28 ± 4), and Latin America (27 ± 5).

DISCUSSION

In this large, racially and geographically diverse cohort with recent subcortical ischemic strokes, significant differences in age, sex, and vascular risk factors between Whites, Blacks and Hispanics emerged. These differences are likely to impact the prognoses for recurrent stroke and cognitive impairment and perhaps the response to blood pressure control and antiplatelet therapies. For example, blood pressure control may offer larger relative benefits to Blacks, who have the highest prevalence of hypertension, compared with Hispanics, who have the highest frequency 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 the cohort.

The differences in stroke risk factors among White, Black, and Hispanic participants reported here are consistent with findings from previous studies and may reflect the ethnic disparities in stroke care.[21] Important to note is the 6 year difference in age of onset of stroke with an average age of 58 years (SD=9.5) for Black participants compared with 64 years for White (SD=10.8) and Hispanic (SD=10.7) participants. 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 in comparison to 65% and 71% for Hispanic and White participants respectively, underscores the important effects of stroke for Blacks on disability-free years. Furthermore, Black participants were more likely to have a history of prior 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 prior to the index stroke. Morgenstern and colleagues reported that only about two-thirds of Mexican Americans were taking antiplatelet medications for secondary stroke prevention in the Brain Attack Surveillance in Corpus Christi (BASIC) Project.[22] Consistent with previous reports, Black participants were significantly more likely to be hypertensive, with a higher blood pressure at trial entry.[23–25] Similar to findings from the BASIC Project,[26] Hispanics had a significantly higher prevalence of diabetes (42%) compared with Whites (32%), while White participants (13%) had a significantly higher prevalence of ischemic heart disease than Hispanic participants (6%). A comparison of the proportion of diabetes in Latin American participants (38%) compared with the proportion in Hispanics overall (42%) suggests that this higher prevalence 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 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 if 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 neuro-imaging (Table 4). These samples are diverse in the country of origin and also in the time they were studied with publications dating from 1989 to 2011. The average age at trial entry for SPS3 participants was 63 years, falling

within the range seen in this series, and consistent with reports of a younger average age for those with lacunar stroke compared to other stroke sub-types.[27–28] There is considerable variability in the prevalence of vascular risk factors across the series. For example, the reported prevalence of hypertension ranged from a low of 41% in the Finnish cohort[29] to a high 88% in the cohort from Germany,[30] with the majority reporting at least 60% prevalence and SPS3 reporting 75%. SPS3 was among those studies reporting the highest prevalence of diabetes. Differences in prevalence may relate to the inconsistencies in how the vascular risk factor was defined as well as the source of the cohort. SPS3 is the only clinical trial in the series. Despite the strict criteria imposed on patient inclusion in a clinical trial, the baseline characteristics of the SPS3 cohort fall within the range reported in these series and provide support that the results from SPS3 will be applicable to the overall population of patients with lacunar stroke.

There is no generally accepted or consistent way that ethnicity is defined across studies[21] and this has been a challenging issue in this study, particularly with the inclusion of sites from Spain and Latin America. We made several assumptions in our classification including that participants from South America were Hispanic and that those 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, the results presented here, highlighting race/ethnic differences, were undertaken for the purpose of describing fully the clinical features of the SPS3 cohort. As they were unadjusted and are cross-sectional, we are unable to draw conclusions regarding the reasons for the differences by race/ethnicity. These unadjusted findings do emphasize the greater prevalence of stroke risk factors in Blacks and Hispanics and also the greater impact on functional recovery at approximately 3 months after the index stroke.

In conclusion, examination of the baseline characteristics in the SPS3 cohort compared with other published lacunar stroke series demonstrates that the cohort is representative of lacunar stroke patients in general. This finding will enhance generalizability of the SPS3 trial results to the millions of patients around the world with this common disorder. Due to its multi-racial cohort, the results of SPS3 should further the understanding of racial/ethnic differences in stroke risk and prevention.

Acknowledgments

References

1. Kolominsky-Rabas PL, Weber M, Gefeller O, et al. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke. 2001; 32:2735–2740. [PubMed: 11739965]

2. Norrving B. Long-term prognosis after lacunar infarction. Lancet Neurol. 2003; 2:238–245. [PubMed: 12849212]

3. Norrving B. Lacunar infarcts: no black holes in the brain are benign. Practical Neurology. 2008; 8:222–228. [PubMed: 18644908]

4. Sacco RL, Kargman DE, Gu Q, et al. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. Stroke. 1995; 26:14–20. [PubMed: 7839388]

5. Worley KL, Lalonde DR, Kerr DR, et al. Survey of the causes of stroke among Mexican Americans in South Texas. Tex Med. 1998; 94:62–67. [PubMed: 9595955]

6. Benavente O, Hart R, Palacio S, et al. Stroke recurrence, cognitive impairment and white matter abnormalities are frequent in Hispanic Americans with lacunar stroke. Cerebrovasc Dis. 2002; 13(suppl 3):87. (abstr).

7. Benavente OR, White CL, Pearce L, et al. The Secondary Prevention of Small Subcortical Strokes (SPS3) study. Int J Stroke. 2011; 6:164–175. [PubMed: 21371282]

8. The ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. 2009; 360:2066–2078. [PubMed: 19336502]

9. The Clopidogrel in Unstable Angina to Prrevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001; 345:494–502. [PubMed: 11519503]

10. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002; 288:2411–2420. [PubMed: 12435254]

11. Gueyffier F, Froment A, Gouton M. New meta-analysis of treatment trials of hypertension: improving the estimate of therapuetic benefit. J Hum Hypertens. 1996; 10:1–8. [PubMed: 8642184]

12. 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. [PubMed: 14576382]

13. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med. 2003; 163:1069–1075. [PubMed: 12742805]

14. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. J Psychiat Res. 1975; 12:189–198. [PubMed: 1202204]

15. Norris J. Comment on "Study design of stroke treatments". Stroke. 1982; 13:527–528. [PubMed: 7101358]

16. Farrell B, Godwin J, Richards S, et al. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry. 1991; 54:1044–1054. [PubMed: 1783914]

17. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J. 1957; 2:200–215. [PubMed: 13432835]

18. Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. Md State Med J. 1965; 14:61–65. [PubMed: 14258950]

19. Lindley RI, Waddell F, Livingstone M, et al. Can simple questions assess outcome after stroke? Cerebrovasc Dis. 1994; 4:314–324.

20. Office of Management and Budget. [Accessed August 2011] Standards for classifcation of federal data on race and ethnicity. http://www.whitehouse.gov/omb/fedreg_race-ethnicity

21. Cruz-Flores S, Rabinstein A, Biller J, et al. Racial-ethnic disparities in stroke care: The American experience: A Statement for Healthcare Professionals From the American Heart Association/ American Stroke Association. Stroke. 2011; 42:2091–2116. [PubMed: 21617147]

22. Morgenstern LB, Smith MA, Lisabeth LD, et al. Excess stroke in Mexican Americans compared with non-Hispanic Whites: the Brain Attack Surveillance in Corpus Christi Project. Am J Epidemiol. 2004; 160:376–383. [PubMed: 15286023]

23. Bravata DM, Wells CK, Gulanski B, et al. Racial disparities in stroke risk factors: the impact of socioeconomic status. Stroke. 2005; 36:1507–1511. [PubMed: 15961710]

24. Cushman M, Cantrell RA, McClure LA, et al. Estimated 10-year stroke risk by region and race in the United States. Ann Neurol. 2008; 64:507–513. [PubMed: 19067365]

25. Sacco RL, Boden-Albala B, Abel G, et al. Race-ethnic disparities in the impact of stroke risk factors. The Northern Manhattan Stroke Study. Stroke. 2001; 32:1725–1731. [PubMed: 11486097]

26. Uchino K, Risser JMH, Smith MA, et al. Ischemic stroke subtypes among Mexican Americans and non-Hispanic whites: the BASIC Project. Neurology. 2004; 63:574–576. [PubMed: 15304600]

27. Arboix A, Marti-Vilalta JL. Lacunar stroke. Expert Rev Neurother. 2009; 9:179–196. [PubMed: 19210194]

28. You R, McNeil JJ, O'Malley HM, et al. Risk factors for lacunar infarction syndromes. Neurology. 1995; 45:1483–1487. [PubMed: 7644045]

29. Melkas S, Putaala J, Oksala NKJ, et al. Small-vessel disease relates to poor poststroke survival in a 12-year follow-up. Neurology. 2011; 76:734–739. [PubMed: 21339501]

30. Wessels T, Rottger C, Jauss M, et al. Identification of embolic stroke patterns by diffusion-weighted MRI in clinically defined lacunar stroke syndromes. Stroke. 2005; 36:757–761. [PubMed: 15746460]

31. Norrving B, Cronqvist S. Clinical and radiologic features of lacunar versus nonlacunar minor stroke. Stroke. 1989; 20:59–64. [PubMed: 2911836]

32. Tegeler CH, Shi F, Morgan T. Carotid stenosis in lacunar stroke. Stroke. 1991; 22:1124–1128. [PubMed: 1819253]

33. Landi G, Cella E, Boccardi E, et al. Lacunar versus non-lacunar infarcts: pathogenetic and prognostic differences. J Neurol Neurosurg Psychiatry. 1992; 55:441–445. [PubMed: 1619408]

34. Toni D, Fiorelli M, De Michele M, et al. Clinical and prognostic correlates of stroke subtype misdiagnosis within 12 hours from onset. Stroke. 1995; 26:1837–1840. [PubMed: 7570735]

35. Salgado AV, Ferro JM, Gouveia-Oliveira A. Long-term prognosis of first-ever lacunar stroke: A hospital-based study. Stroke. 1996; 27:661–666. [PubMed: 8614926]

36. Yip PK, Jeng JS, Lee TK, et al. Subtypes of ischemic stroke. A hospital-based stroke registry in Taiwan (SCAN-IV). Stroke. 1997; 28:2507–2512. [PubMed: 9412641]

37. Martí-Vilalta JL, Arboix A. The Barcelona Stroke Registry. Eur Neurol. 1999; 41:135–142. [PubMed: 10202244]

38. Awada A, Al Rajeh S. The Saudi Stroke Data Bank. Analysis of the first 1000 cases. Acta Neurol Scand. 1999; 100:265–269. [PubMed: 10510688]

39. Hajat C, Dundas R, Stewart JA, et al. Cerebrovascular risk factors and stroke subtypes: differences between ethnic groups. Stroke. 2001; 32:37–42. [PubMed: 11136911]

40. Yokota C, Minematsu K, Hasegawa Y, et al. Long-term prognosis, by stroke subtypes, after a first-ever stroke: a hospital-based study over a 20-year period. Cerebrovasc Dis. 2004; 18:111–116. [PubMed: 15218275]

41. Soda T, Nakayasu H, Maeda M, et al. Stroke recurrence within the first year following cerebral infarction--Tottori University Lacunar Infarction Prognosis Study (TULIPS). Acta Neurol Scand. 2004; 110:343–349. [PubMed: 15527445]

42. Bejot Y, Catteau A, Caillier M, et al. Trends in incidence, risk factors, and survival in symptomatic lacunar stroke in Dijon, France, from 1989 to 2006: a population-based study. Stroke. 2008; 39:1945–1951. [PubMed: 18436869]

43. Turin TC, Kita Y, Rumana N, et al. Ischemic stroke subtypes in a Japanese population: Takashima Stroke Registry, 1988–2004. Stroke. 2010; 41:1871–1876. [PubMed: 20689083]

44. Wardlaw JM, Doubal FN, Eadie E, et al. Little association between intracranial arterial stenosis and lacunar stroke. Cerebrovasc Dis. 2011; 31:12–18. [PubMed: 20980748]

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 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 3 months
Diabetes	Present if either of the following criteria was met:

		• chronic elevation of the fasting serum glucose exceeding 120 mg/dl or chronic requirement for hypoglycemic medications • reporting anti-hypoglycemic 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 MI • 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 LV wall-motion abnormality • angiographic evidence of coronary occlusive disease with associated ventricular dys-synergy 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 patient has undergone an invasive cardiac procedure for the treatment of anginal symptoms (i.e., PTCA or CABG)
	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 LV 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 lab data confirming fasting hyperlipidemia.

Appendix 2. Country and clinical site (number of enrolled patients)

USA, 50 sites (n=1,677): 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); The 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); The 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); The 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); John 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 Sunny-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); The Regents of the University of California, Fresno, CA (4); Loyola University of Chicago, IL (4); Indiana University, Indianapolis, IN (2); University of Illinois at 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 (171); CHILE, 2 sites (n= 127): Hospital Naval Almirante Nef, Viña del Mar (69); Hospital Clínico Universidad Católica de Chile, Santiago (58); MÉXICO, 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); PERÚ, 1 site (n=186): Fundación Cayetano Heredia, Lima (186); 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).
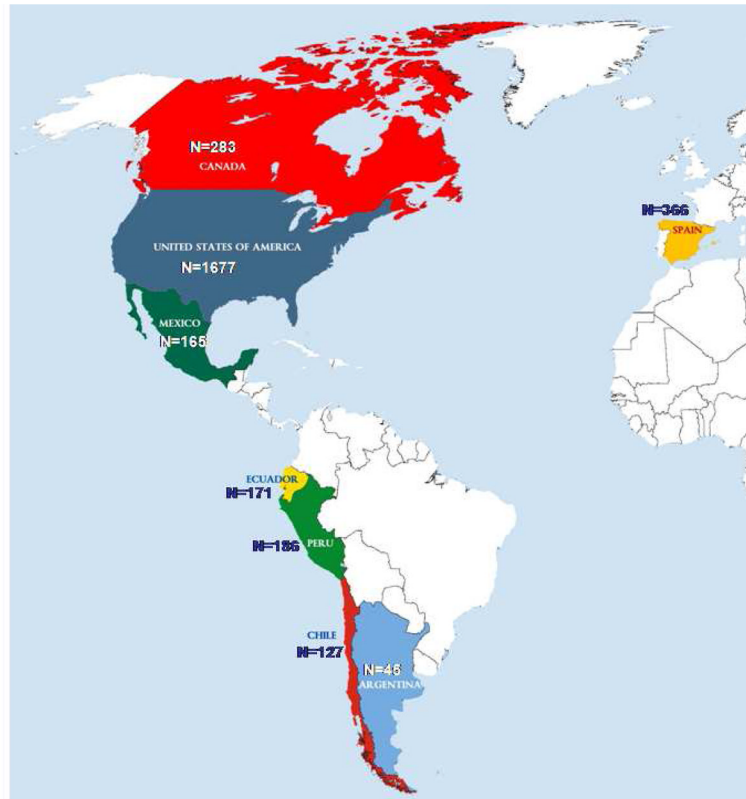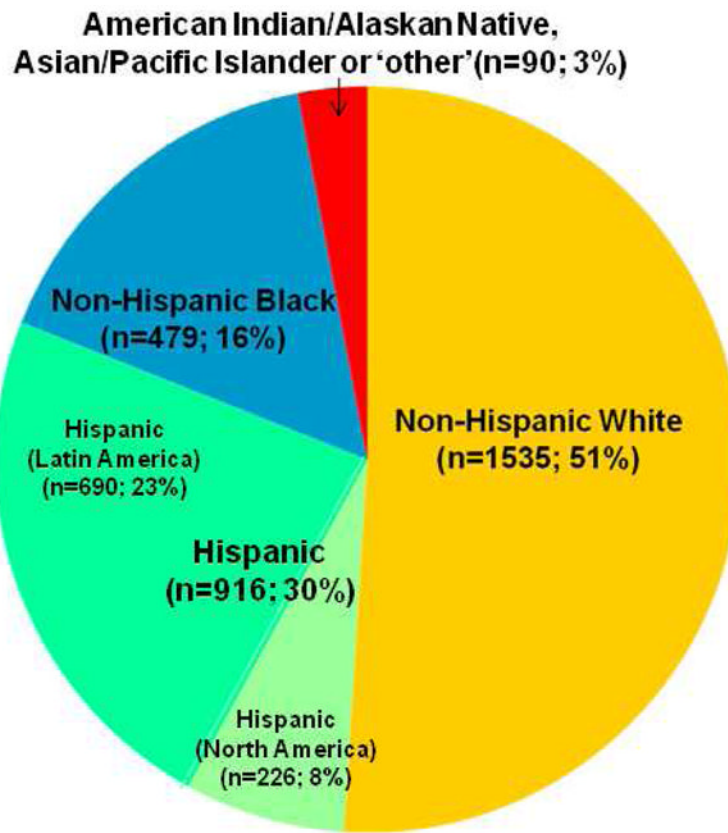
Figure 1.
Randomization by Country

Figure 2.
Racial/Ethnic Distribution

Table 1

Demographic and clinical characteristics of study participants

	Overall (n=3020)	Non-Hispanic White (n=1538)	Hispanic (n=916)	Non-Hispanic Black[1] (n=492)
Mean age, years	63 ± 11	64 ± 10.8	64 ± 10.7	58 ± 9.5[**]
Male, %	63	65	63	54[**]
Lifestyle behaviors prior to 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, mean times per week	3.1 ± 3	4 ± 3	2 ± 2.8[**]	2 ± 2.7[**]
Medical history prior to 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
Prior symptomatic small subcortical stroke	10	9	12	13[*]
Prior 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 prior to qualifying event, %	31	37	22[**]	32
Aspirin used regularly in 7 days prior to 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

	Overall (n=3020)	Non-Hispanic White (n=1538)	Hispanic (n=916)	Non-Hispanic Black[1] (n=492)
Other	11	11	12	6

Data are presented as percentages or mean ± SD

*
significantly different from Non-Hispanic White population at p 0.01

**
significantly different from Non-Hispanic White population at p 0.001

[1]includes 22 patients who also reported Hispanic ethnicity

Table 2

Selected clinical characteristics measured at trial entry

	Overall (n=3020)	Non-Hispanic White (n=1538)	Hispanic (n=916)	Non-Hispanic Black[1] (n=492)
Functional recovery[2]				
Barthel Index 95, %	80	86	68[**]	83
Rankin score of 0–1, %	67	71	65[**]	55[**]
Mean body mass index	29.1 ± 6.8	29 ± 5.8	28 ± 5.7[*]	31 ± 10.6[**]
Mean systolic blood pressure (mmHg)	143 ± 19	141 ± 17.2	144 ± 20[**]	147 ± 19.9[**]
Mean diastolic blood pressure (mmHg)	78 ± 11	77 ± 9.9	79 ± 11[**]	82 ± 11.6[**]
Medications at time of trial entry				
Anti-hypertensive medications, %	85	83	84	92[**]
Angiotensin-converting enzyme inhibitor, %	52	49	55[*]	58[**]
Diuretics, %	36	36	26[**]	56[**]
Calcium channel blockers, %	26	23	24	38[**]
Beta blockers, %	25	25	17[**]	37[**]
Angiotensin-receptor blocker, %	16	17	18	9[**]
Lipid-lowering medications, %	73	76	65[**]	76
Statins, %	69	72	61[**]	72
Hypoglycemic medications, %	33	28	39[**]	37[**]
Selected laboratory values				
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[**]
LDL cholesterol (mg/dl)	108 ± 45.7	106 ± 47.4	105 ± 42.8	120 ± 43.4[**]
HDL 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[**]

Data are presented as percentages, mean ± SD, or median (interquartile range)

[*] significantly different from Non-Hispanic White population at p 0.01

[**] significantly different from Non-Hispanic White population at p 0.001

[1] includes 22 patients who also reported Hispanic ethnicity

[2] Barthel Index ranges from 0 to 100 with higher scores indicating better function; Rankin Score ranges from 0 to 6 with lower scores indicating better function

LDL (low-density lipoprotein); HDL (high-density lipoprotein);

Table 3

Selected demographic and clinical characteristics stratified by geographic region

	North America[1] (n=1960)	Latin America[1] (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[2]	488 (24.9)	4 (0.6)	0
Other[3]	74 (3.8)	0	0
Mean age, years[*]	62 ± 11	66 ± 11	65 ± 11
Male, %[*]	60	65	75
Lifestyle behaviors prior to 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, mean times per week[*]	3 ± 3	2 ± 3	5 ± 3
Medical history prior to 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
Prior symptomatic small subcortical stroke	10	11	8
Prior 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
Rankin score of 0–1, %	67	64	67
Barthel Index 95, %[*]	85	64	84
Mean body mass index[*]	30 ± 7.5	27 ± 5	28 ± 4
Mean systolic blood pressure (mmHg)[*]	143 ± 19	144 ± 21	139 ± 16
Mean diastolic blood pressure (mmHg)	78 ± 11	79 ± 12	78 ± 9

	North America[1] (n=1960)	Latin America[1] (n=694)	Spain (n=366)
Anti-hypertensive medications, %[*]	87	84	75
Lipid-lowering medications, %[*]	77	62	72
Hypoglycemic medications, %	33	34	34

Data are presented as percentages, mean ± SD, or median (interquartile range)

[*] difference among groups significant at p <0.01

[1] North America (United States and Canada); Latin America (Mexico, Ecuador, Peru, Chile, and Argentina)

[2] includes 22 patients (18 in North America and 4 in Latin America) who also reported Hispanic ethnicity

[3] Other includes those who reported their race as American Indian/Alaskan Native, Asian/Pacific Islander, or 'other'

Table 4

Lacunar stroke series

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

Data are presented as mean ± SD or percentage

HTN (hypertension), DM (diabetes mellitus), IHD (ischemic heart disease), PVD (peripheral vascular disease), TIA (transient ischemic attack), HPL (hyperlipidemia), NR (not reported), NA (North America), LA (Latin America)

*
6 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