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The Secondary Prevention of Small Subcortical Strokes (SPS3) study

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Abstract

Background—Small subcortical strokes, also known as lacunar strokes, comprise more than 25% of brain infarcts, and the underlying vasculopathy is the most common cause of vascular cognitive impairment. How to optimally prevent stroke recurrence and cognitive decline in S3 patients is unclear. The aim of the Secondary Prevention of Small Subcortical Strokes study (Trial registration: NCT00059306) is to define strategies for reducing stroke recurrence, cognitive decline, and major vascular events.

Methods—Secondary Prevention of Small Subcortical Strokes is a randomised, multicentre clinical trial ($n = 3000$) being conducted in seven countries, and sponsored by the US NINDS/

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NIH. Patients with symptomatic small subcortical strokes in the six-months before and an eligible lesion on magnetic resonance imaging are simultaneously randomised, in a 2 × 2 factorial design, to antiplatelet therapy – 325 mg aspirin daily plus 75 mg clopidogrel daily, vs. 325 mg aspirin daily plus placebo, double-blind – and to one of two levels of systolic blood pressure targets – ‘intensive’ (<130 mmHg) vs. ‘usual’ (130–149 mmHg). Participants are followed for an average of four-years. Time to recurrent stroke (ischaemic or haemorrhagic) is the primary outcome and will be analysed separately for each intervention. The secondary outcomes are the rate of cognitive decline and major vascular events. The primary and most secondary outcomes are adjudicated centrally by those unaware of treatment assignment.

Conclusions—Secondary Prevention of Small Subcortical Strokes will address several important clinical and scientific questions by testing two interventions in patients with recent magnetic resonance imaging-defined lacunar infarcts, which are likely due to small vessel disease. The results will inform the management of millions of patients with this common vascular disorder.

Keywords

antiplatelet therapy; hypertension; lacunar stroke; randomised clinical trial; SPS3

Background

Small subcortical strokes (S3), also known as lacunar infarcts, comprise about 25% of ischaemic strokes (1–3), are particularly frequent in Hispanics (4–11), and tend to occur at a younger age than other stroke subtypes (12). The underlying vascular pathology is a common cause of cognitive impairment (13–14). While any aetiology of brain ischaemia (e.g. cardiogenic embolism or carotid stenosis) can occasionally cause S3, most result from intrinsic diseases of the small penetrating arteries. The frequent coexistence of multiple S3 and extensive white matter hyperintensities on magnetic resonance imaging (MRI) supports the belief that both conditions share a common mechanism: cerebral small vessel disease (15–17). Despite their frequency and importance, no clinical trial has focused on this stroke subtype (18).

Prospective studies of S3 describe a stroke recurrence rate of 4–11% per year (19–23), comparable to other common types of cerebral ischaemia (24). About 50% of recurrent strokes in S3 patients are also S3, supporting a distinctive pathomechanism (24). The presence of white matter hyperintensities on neuroimaging studies of S3 patients may be an indicator of the severity and extent of small vessel disease, and appears to predict a higher rate of recurrent stroke (25).

While S3s usually result in relatively mild disability, S3 is the most common stroke subtype associated with cognitive impairment and vascular dementia (13–14, 26). The MRI evidence of extensive white matter abnormalities increases significantly the risk of vascular dementia (27–29). The estimated rate of cognitive impairment and/or vascular dementia in S3 patients is 3–5% per year (25, 30). We hypothesise that interventions that reduce stroke recurrence may also prevent cognitive decline in S3 patients.

Hispanics appear to have a higher prevalence of small cerebrovascular disease, with S3 the most frequent stroke subtype (30–40% of ischaemic strokes) (10, 31–34). While a higher prevalence of diabetes mellitus could contribute to this propensity, Hispanic ethnicity appears to incur an increased risk of S3 (10).

Antiplatelet agents and prevention of recurrent S3

Despite the distinct pathogenic mechanisms of strokes caused by small vessel disease, no randomised trial has independently assessed the value of antiplatelet agents in an MRI-defined group of patients with S3 (18). Subgroup analyses of participants with lacunar infarcts (vaguely defined) in four randomised trials support the use of antiplatelet therapy in this stroke subtype (35–38) and suggest that antiplatelet therapy may be particularly efficacious for patients with S3. There is no direct evidence that one antiplatelet agent or a combination of agents is more effective than another. For example, the recent Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS) trial randomised 22 322 patients with recent ischaemic stroke, of whom about 50% were classified as having a lacunar stroke at entry, and reported similar results for two different antiplatelet regimens regardless of stroke subtype (i.e. presumed lacunar vs. large vessel strokes) (39).

The results from these clinical trials provide the rationale for hypothesising that combined antiplatelet therapy may confer additional benefit for S3 patients. Aspirin and clopidogrel are both platelet antiaggregant agents, albeit with different mechanisms of action. Both agents have been tested separately and have been shown to be effective for the secondary prevention of ischaemic stroke. The rationale for the use of clopidogrel in combination with aspirin is based on their complementary mechanisms of action. The enhanced efficacy of this combination compared with aspirin alone for the prevention of vascular events has been demonstrated in several randomised trials (40–43). At present, there is no definitive answer as to what is the optimal antiplatelet strategy for stroke prevention in patients with S3 due to small vessel disease.

Optimal control of blood pressure following S3

Hypertension is the most prevalent and powerful modifiable risk factor for stroke in general and particularly for S3, and yet relatively little is known about the optimal target levels of blood pressure control for secondary stroke prevention. In pooled analyses of subgroups of patients with stroke and transient ischaemic attack (TIA) included in clinical trials, blood pressure lowering with antihypertensive drugs reduced recurrent stroke by about 28% (44–46). The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) randomised 6600 patients with prior stroke or TIA to receive perindopril with or without a thiazide diuretic in addition to usual antihypertensive therapy (47). The average achieved difference in systolic blood pressure of 9 mmHg was associated with a 28% reduction in recurrent stroke, with similar results for the approximately one-third of participants with ‘lacunar stroke’ (48). Although PROGRESS provides important reassurance that lowering blood pressure after stroke is generally safe and importantly reduces recurrent stroke, it does not provide clear guidance about optimal target levels.

Recently, the Action to Control Cardiovascular Risk in Diabetics (ACCORD) trial tested intensive (< 120 mmHg) vs. standard (< 140 mmHg) blood pressure control in adults with type 2 diabetes, and one or more vascular risk factors or diagnosed vascular disease ($n = 4722$) (49). The mean achieved systolic blood pressures after one-year of follow-up in the randomised groups were 119 vs. 134 mmHg, respectively. Primary outcome (first of stroke, myocardial infarction or vascular death) rates, assessed after a mean follow-up of 4.7 years, were not significantly different between treatment groups (2.1% vs. 1.9% per patient-year, respectively) but stroke was decreased by 41%, albeit delayed for one- to two-years.

Cognitive decline in the elderly has been shown to be inversely related to blood pressure control (50). Secondary analysis of the Systolic Hypertension in Europe (Syst-Eur) Trial, involving elderly patients with isolated systolic hypertension, showed reduced cognitive decline in those actively treated vs. no treatment independent of recurrent clinical stroke (51). Cognitive outcome results from PROGRESS as assessed using the Folstein Mini-Mental Status Exam showed that patients on active treatment had a nonsignificantly reduced risk of dementia (RRR: 12%; 95% CI: -8% to 28%) and a significantly reduced risk of cognitive decline (RRR: 19%; 95% CI: 4–32%) associated with recurrent stroke (52).

Whether specific types of antihypertensive agents offer benefit for stroke reduction, independent of their effects on blood pressure lowering, is controversial. For example, angiotensin converting enzyme (ACE) inhibitors have been postulated to have effects on vascular endothelium that provide additional protection against vascular events (53). The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) directly compared four different classes of antihypertensive agents in patients with hypertension without prior stroke and showed similar event rates among the antihypertensive agents (54). Whether a particular class of antihypertensive agent offers a particular advantage for use in stroke prevention remains unclear (46).

Evidence supports lowering of blood pressure for the prevention of stroke. How much the clinical effects of lowering blood pressure, as defined in clinical trials of primary prevention, applies directly to patients with S3 and cerebral small vessel disease is uncertain, and the optimal level of blood pressure control remains unknown. We contend that 'intensive' lowering of blood pressure for reducing recurrent stroke and cognitive decline must be assessed specifically in S3 patients, most of whom have cerebral small vessel disease. The penetrating arteries are end-arteries without collateral anastomoses. How hypertension control affects clinical outcomes in the presence of small vessel disease cannot be determined by considering all pathogenetic types of ischaemic strokes together. At the present time, an absolute target blood pressure for stroke reduction is uncertain, and these targets should be established based on the results of randomised trials (55).

Study aims

The aim of the Secondary Prevention of Small Subcortical Strokes (SPS3) study is to define efficacious therapies for patients with cerebral small vessel disease and its two most common clinical manifestations: small subcortical strokes (lacunar strokes) and cognitive decline (vascular dementia). Specifically, SPS3 tests, in parallel, whether combination

antiplatelet therapy consisting of aspirin plus clopidogrel is superior to aspirin alone and also whether 'intensive' blood pressure lowering is superior to 'usual' blood pressure management for reducing stroke recurrence (primary endpoint), cognitive decline, and major vascular events. A secondary aim is to compare differences in the absolute benefit of these interventions on recurrent stroke, cognitive decline, and vascular events between Hispanic and non-Hispanic White participants.

Methods

Study design

SPS3 is a randomised, multicentre clinical trial, sponsored by the US NINDS/NIH, being conducted in clinical centres throughout North America, Latin America, and Spain. Patients with a recent (within 180 days) symptomatic S3 who are without surgically amenable carotid artery disease or major-risk cardioembolic sources are randomised, in a 2×2 factorial design, to both an antiplatelet intervention and to a target level of systolic blood pressure control. Target enrolment is 3000 participants (or until April 2011, whichever comes first), and participants will be followed, on average, for about four-years. Planned enrolment of Hispanic patients is 20% of the total enrolment.

Study population

Inclusion and exclusion criteria—SPS3-eligible patients have a symptomatic S3 with MRI confirmation (Table 1). The patient must be randomised within six-months of the qualifying S3, and each of the following criteria must be met:

- clinical lacunar stroke syndrome (modified from the Fisher criteria) (56)
- absence of signs or symptoms of cortical dysfunction
- no ipsilateral cervical carotid stenosis ($\geq 50\%$) if the qualifying event is hemispheric, and
- no major-risk cardioembolic source requiring anticoagulation or other specific therapy (minor-risk cardioembolic sources are allowed if anticoagulation is not prescribed).

Lacunar TIAs require positive MRI diffusion imaging to be eligible (i.e. meeting the revised American Heart Association definition for stroke) (57). The MRI must show no evidence of recent or remote cortical infarct, large (>1.5 cm subcortical infarct, or prior intracerebral haemorrhage (the presence of microbleeds is not an exclusion). The MRI must demonstrate at least one of the following four specific criteria:

- diffusion-weighted imaging (DWI) lesion ≥ 2.0 cm in size at the largest dimension (including the rostro-caudal extent) with a positive apparent diffusion coefficient (ADC) image, and corresponding to the clinical syndrome
- well-delineated focal hyperintensity ≥ 2.0 cm in size at the largest dimension (including the rostro-caudal extent) on fluid-attenuated inversion recovery (FLAIR) or T2 and clearly corresponding to the clinical syndrome. If DWI is negative and

the study was carried out within 30 days after the index event, this criterion alone is not sufficient for study entry

- multiple (at least two) hypointense lesions 0.3–1.5 cm in size at the largest dimension (including the rostro-caudal extent) only in the cerebral hemispheres on FLAIR or T1 in patients whose qualifying event is clinically hemispheric. If the qualifying event is clinically brainstem or cerebellar, this criterion alone is not sufficient for study entry, and
- well-delineated hypointense lesion ≥ 1.5 cm in size at the largest dimension (including the rostro-caudal extent) on FLAIR or T1 corresponding to the clinical syndrome with the MRI carried out at least one-month after the qualifying stroke.

Eligibility on MRI is determined by a local investigator based on the MRI obtained for patient diagnostic purposes. MRIs are not obtained with a prespecified data acquisition protocol. De-identified images are then submitted to the Coordinating Center and centrally interpreted by a neuroradiologist, who is unaware of patient features, to confirm patient eligibility and collect data on the prevalence of lacunar infarcts, microbleeds, and white matter disease. Acute lacunar infarcts are defined as well-circumscribed bright lesions on DWI with positive ADC or areas of increased signal on FLAIR or T2 with a size up to 2 cm in all dimensions, located in the subcortical white or grey matter, cerebellar white matter, or brain stem. A subacute or a chronic lacunar infarct is defined as a cavitated lesion seen on T2 or FLAIR located in the same regions measuring between 3 mm and 15 mm in maximum dimensions. If the lesions are located in the anterior commissure or inferior putamen with a dimension < 3 mm, these are termed perivascular spaces. Microbleeds are diagnosed on T2 gradient echo and classified according to the Brain Observer MicroBleed Scale (58). White matter disease is graded using the Age-Related White Matter Changes scale (59) and the Fazekas scale (60).

Study entry procedures

Investigations to determine eligibility include an MRI, electrocardiography, transthoracic or transoesophageal echocardiography, and standard laboratory blood tests. Results from investigations performed at the time of the stroke can be used to determine eligibility. Imaging of the cervical and intracranial arteries is also required (usually MR or CT angiography) and is graded using the North American Symptomatic Carotid Endarterectomy Trial criteria (61). Results of intracranial arterial imaging do not preclude trial eligibility but are used to identify participants with associated large artery disease for subgroup analyses.

Patients undergo at least two study visits to complete all prerandomisation procedures. Demographic and medical history data are collected, as well as information regarding ethnicity and race. Patients who identify as Spanish/Hispanic/Latino in origin report information based on the San Antonio Heart Study Classification (62). Participants self-report race as one or more of the following: White; Black, African-American, or Negro; American Indian or Alaska Native; Asian or Pacific Islander; Mestizo; Mulato; or other. Patients are screened for cognitive dysfunction using the Folstein Mini Mental Status Examination (63), and an SPS3-certified examiner administers a detailed cognitive assessment. A standardised neurological exam is performed (64), functional ability is

assessed using the modified Rankin score (65, 66) and the Barthel Index (67), and current medications are recorded. Blood pressure is measured following the SPS3 protocol (Table 2) at each of the two prerandomisation study visits for classification of hypertensive status. Participants classified as hypertensive at study entry meet at least one of the following two criteria; first, a definite history of hypertension before stroke and currently receiving antihypertensive medications, and second, the average blood pressure measurement obtained from the two prerandomisation visits at study entry is at least 140 mmHg systolic and/or at least 90 mmHg diastolic, regardless of concurrent anti-hypertensive medications. Eligible patients may be randomized at the second visit, which must be at least two-weeks after the qualifying stroke.

The detailed cognitive assessment (Table 3) is carried out by licensed clinical psychologists, graduate students of neuropsychology, or other qualified personnel, each of whom must complete a certification process to show familiarity and competence with the neuropsychological tests being used in SPS3 before testing SPS3 patients. Sessions are audio-taped and submitted along with test forms to the Coordinating Center for quality assurance purposes. Examiners are unaware of treatment assignments.

Randomisation

Patients are randomised simultaneously, in a 2×2 factorial design, to both an antiplatelet intervention and to a target level of systolic blood pressure control (Fig. 1). Randomisation assignments – stratified by clinical centre and baseline hypertensive status (hypertensive or normotensive) – are generated using a permuted-block design (variable block size), are stored in each clinical centre's electronic data entry system, and are protected from preview. At the time of randomisation, the study coordinator enters patient-specific information into the data entry system, including age, date of birth, date of qualifying S3, confirmation that each inclusion criteria is met and none of the exclusion, and dates of key study procedures. If the patient is study-eligible, a unique study identification number for the patient and systolic blood pressure target group are assigned. Assigned study identification number corresponds to the label number on the bottle of study drug (clopidogrel 75 mg or matching placebo) that the patient receives.

Interventions

Antiplatelet intervention—All SPS3 participants take enteric-coated aspirin 325 mg daily and are randomly assigned (double-blind) to take clopidogrel 75 mg daily or the matching placebo. Antiplatelet medications are provided to patients at randomisation and each quarterly follow-up visit, with adherence measured by pill counts. Patients are educated about contraindicated medications (i.e. nonstudy aspirin, clopidogrel, or anticoagulants) while on SPS3 antiplatelet therapy.

Blood pressure intervention—Patients are randomised to either 'intensive' (<130 mmHg) or 'usual' (130–149 mmHg) systolic blood pressure targets. This arm is not blinded due to the challenges of blinding while managing blood pressure into specific targets. The Prospective, Randomized, Open-label, Blinded Endpoint (PROBE) study design (68), a standard for international blood pressure trials, is being utilised (69–71). This design

preserves the benefits of randomisation while reducing bias in the ascertainment of outcomes through blinded end-point detection.

Sites are provided with the Colin 8800C (Colin Medical Instruments, an Onrom Company, San Antonio, TX, USA), an automated oscillometric electronic device for blood pressure measurement, which meets the Association for the Advancement of Medical Instrumentation standards (72, 73). Blood pressure is measured according to a detailed protocol (Table 2) based on Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) guidelines (74), and all site personnel receive instruction on the protocol before initiating the trial. The automated blood pressure device and standard protocol minimises potential investigator bias in the determination of blood pressure.

Participant blood pressure is managed locally at each clinical centre by a physician with expertise in blood pressure management. A recommended algorithm, based on JNC-VII guidelines (74), is provided to all sites to assist with blood pressure management (<http://www.sps3.org>). The algorithm advocates titration of dose, as well as the addition of agents, using a step-wise approach, monitoring carefully for specific side effects of agents or due to lowering of blood pressure. Patients are seen at least monthly for adjustment of antihypertensive medications to achieve the assigned target blood pressure. Once the systolic blood pressure is in the assigned target range at two consecutive visits, the participant continues with quarterly follow-ups. To maximise adherence, blood pressure medications are provided free of charge to participants as deemed appropriate by the site hypertension expert. One or two drugs from each of the major classes of antihypertensive medications and additional medications on a case-by-case basis are available.

Normotensive patients at study entry who become hypertensive during follow-up are managed according to their assigned blood pressure targets. Drugs to increase blood pressure are not administered, to achieve the 130–149 target, for those participants whose systolic blood pressure is <130 mmHg and are not on blood pressure-lowering medications. Antihypertensive drugs prescribed to participants for reasons other than blood pressure control (e.g. β -blockers after myocardial infarction or ACE inhibitors for diabetic nephropathy) are not discontinued in order to achieve the assigned blood pressure target.

Follow-up procedures

All participants, including those who experience an event, or who discontinue one or both assigned SPS3 interventions, are seen at least monthly for the initial three-months after randomisation and thereafter on a quarterly basis until a common study end date. Blood pressure is measured, study medications are dispensed, and adherence to study therapies is monitored. A standard set of questions is administered to help assess for medication side effects and adverse events and to detect outcome events. A standardised interview questionnaire to detect symptoms of TIA and stroke is administered to all patients by the research coordinator at every quarterly follow-up.

At annual visits and at the end of the study visit, in addition to quarterly follow-up procedures, cognitive testing by the SPS3-certified examiner is conducted. The quality of life instruments; Subjective Symptom Assessment Profile (SSA-P) (75) and Stroke-Specific

Quality of Life Scale (SS-QOL) (76) are administered. Functional status is measured using the Instrumental Activities of Daily Living (IADL) scale (77, 78), and assessment for depression is carried out using the Patient Health Questionnaire (79, 80). A lipid profile and serum creatinine are obtained for all participants, and HbA_{1c} for diabetic patients. Management of concomitant risk factors such as diabetes and hyperlipidemia is primarily the responsibility of the participant's primary care physician. A 24 h ambulatory blood pressure procedure is obtained at select sites when participants achieve the assigned target systolic blood pressure.

Study outcome and safety events

The primary outcome in SPS3 is the time to recurrent stroke [first of fatal or nonfatal ischaemic stroke or central nervous system (CNS) haemorrhage]. Ischaemic stroke is clinically defined as a focal neurological deficit persisting for greater than 24 h and is ascertained via clinical evaluation and use of CT or MRI. Ischaemic strokes, restricted to worsening neurological deficits associated with the qualifying or other prior stroke, must meet at least one of the two following criteria: first, no major metabolic derangement that could 'unmask' prior focal deficits and an objective change in neurological exam by an SPS3 neurologist, and second, unequivocally positive DWI indicative of acute ischaemia. The CNS haemorrhage is defined as primary intracranial bleeding of any type documented by neuroimaging, CSF exam, or autopsy. These can be spontaneous, traumatic, or associated with underlying lesions (i.e. aneurysms, arteriovenous malformations, or amyloid angiopathy) and include intraparenchymal, subdural, epidural, intraventricular, and subarachnoid locations. All possible clinical stroke events are assessed at the clinical site by both the local neurology investigator and a neurologist blinded to the assigned treatment arms.

Secondary outcomes include:

- rate of cognitive decline as measured by the Cognitive Assessment Screening Instrument (CASI) (81)
- TIA, defined as an acute focal neurologic deficit due to cerebral ischaemia that resolves completely within 24 h, regardless of neuroimaging findings
- acute myocardial infarct, defined by standard criteria consisting of ECG and cardiac enzyme changes requiring acute hospitalisation
- non-CNS thromboembolism, and
- death, classified as vascular or nonvascular.

Safety events are:

- major cognitive decline, defined as a decline in the CASI score of ≥ 10 points since study entry and sustained on repeat testing, and associated with functional deterioration/ behavioural changes that are not explained by a recent stroke
- major extracranial (systemic) haemorrhage, defined as serious or life-threatening bleeding requiring transfusion of red blood cells or surgery, or resulting in

permanent sequelae or death. Retinal haemorrhages are included if residual visual impairment persists more than three-months after onset

- serious complication of hypotension, defined as a medical event that is directly related to interventions to lower blood pressure, stipulated by the study protocol, which results in urgent medical evaluation, or has the potential to seriously threaten health, or causes persistent/irreversible effects on health status and is not due to the side effects of an antihypertensive agent, and
- other SPS3-related serious adverse event: a serious health problem not captured by any of the above categories that is possibly or probably related to SPS3 interventions and results in at least one of the following outcomes: death, life-threatening, in-patient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or incapacity, or any other important medical event that jeopardises the patient or requires intervention to prevent any of the above.

All possible outcome and safety events are reviewed by the blinded Events Adjudication Committee made up of neurologists, cardiologists, and internists who are not otherwise involved in SPS3. Event materials, including diagnostic information, blinded to patient identity are submitted by the clinical sites to the Events Coordinator, who blinds them to any information potentially revealing SPS3 treatment assignments and distributes to at least two committee members for review.

Data entry

Data are entered by clinical site personnel and transferred from the clinical centres to the Statistical Center on a daily basis using the client/server-based data entry system. The data entry system is an interactive database describing the status of research data, tracking the presence of forms and information, and monitoring the validity of individual data items on the forms. No patient-identifying information is stored at the Statistical Center. All clinical site personnel using the data entry system must first demonstrate proficiency with the system before receiving access to the live database. Data are secure from external violation by limiting access to the computer systems with study data and by password protection.

Statistical analysis plan and sample size calculations

Initially, a sample size of 2500 patients was calculated, assuming an average follow-up of three-years, an estimated three-year recurrent stroke rate of 21%, a 25% relative risk reduction in stroke by combination treatment, a type I error of 0.05, and a type II error of 0.10 (90% power) (82). This corresponds to a 5.25% absolute reduction in the three-year event rate by combination treatment. The sample size of 2500 allowed sufficient power to detect at least a similar reduction in stroke due to intensive blood pressure lowering, although prior studies suggested an even larger decrease in stroke due to intensive blood pressure lowering (47). An unplanned sample size re-estimation was performed midway through randomisation to assess power based on the overall observed event rate in the study (83), and a recommendation was made, to increase the sample size from 2500 to 3000 patients, to the study Data and Safety Monitoring Board (DSMB) and NINDS. After

approval, design modifications were implemented to help ensure sufficient power to detect the 25% relative risk reduction.

Primary analyses consider each arm separately, and will assess treatment differences via standard time-to-event statistical methods. Specifically, each treatment arm will be assessed using the log-rank test. In the unlikely event that an imbalance exists between important covariates at baseline (such as disease severity or age), the Cox proportional hazards model will be used to adjust for these factors. Based on prior data, we have assumed no interaction between treatment arms for the primary analyses; however, we will evaluate the interaction and, if one exists, stratify appropriately and utilise Bonferroni's correction to adjust for multiple comparisons.

Two planned interim analyses are scheduled to occur after one third and two thirds of the primary events have occurred, with results presented to the DSMB. In order to maintain the maximum power for the final analyses, and to simultaneously protect the overall type I error rate of the study, Haybittle–Peto bounds will be used. In addition, futility analyses using conditional power are planned for the times of the interim analyses (84).

Subgroup analyses

Several subgroup analyses for the primary outcome are planned. For the antiplatelet intervention, the following subgroup analyses are proposed:

- Hispanic vs. non-Hispanic White participants
- those taking aspirin at the time of their qualifying stroke (aspirin-failures) compared with those not taking aspirin
- diabetic participants vs. nondiabetics
- those with intracranial stenosis vs. those without intracranial stenosis, and
- those with a high likelihood of cerebral small vessel disease based on vascular imaging and multiplicity of S3 on MRI compared with those with a low likelihood.

For the blood pressure intervention, the following subgroup analyses are planned:

- Hispanic vs. non-Hispanic White participants
- diabetic participants compared with nondiabetics
- those who are normotensive at entry compared with those who are hypertensive at entry
- those with intracranial stenosis vs. those without intracranial stenosis, and
- participants with a high likelihood of cerebral small vessel disease based on vascular imaging and multiplicity of S3 on MRI compared with those with a low likelihood.

Additionally, the impact of the interventions on the primary outcome will be examined more specifically in the following subgroups, based on race and ethnicity:

- White vs. Black vs. Mestizo (excluding Others, Mulato, Natives, and Asian/Pacific Islanders)
- North Americans (minus Hispanics) plus Europeans compared with Latin America plus North American Hispanics, and
- North American Whites minus Hispanics vs. North American Blacks vs. North American Hispanics.

Protection of human subjects

All clinical sites are required to comply with their local Institutional Review Boards and Human Subject Protection policies. All participants provide written informed consent in their preferred language (English, French, or Spanish) before undergoing any study procedures.

The safety of all participants is closely monitored. All safety events are transmitted in real time to an independent Medical Safety Monitor (blinded to treatment arm unless information on treatment assignment is required to ensure participant safety), who expeditiously reviews the data to observe for possible trends in risk and conveys any concerns promptly to the DSMB. The independent DSMB, appointed by NINDS, provides oversight to the trial and reviews study performance twice a year, including safety events, to protect the interest of the study participants during the trial.

SPS3 organisation

The SPS3 Coordinating Center, currently located at the University of British Columbia, Vancouver, Canada (formerly located at University of Texas Health Science Center at San Antonio), is responsible for overseeing the clinical, regulatory, and budgetary activities of the trial including; addressing clinical and methodological questions from the clinical centres, identifying and responding to issues related to study interventions and follow-up, central review of imaging data, central storage and quality control of cognitive data, and budget operations. The Statistical Center, located at the University of Alabama, Birmingham, oversees randomisation assignments, data entry and management, statistical analyses, study execution reports, and study reports for the DSMB. The Drug Distribution Center – at the VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center in Albuquerque, New Mexico – packages the blinded study medication, maintains medication inventory, and supplies the clinical sites with study medication and antihypertensive medications. Each of the clinical sites has a core team consisting of a neurologist, a hypertension physician specialist, and a research coordinator, all who receive in-depth standardised training on the SPS3 protocol before beginning the study. Operations, Executive, and Steering Committees provide guidance and oversight to the trial including design, management, and budgetary issues.

Substudies

Two substudies are nested within SPS3. The Levels of Inflammatory Markers in the Treatment of Stroke study is investigating whether serum levels of hsCRP, serum amyloid

A, IL6, CD40 ligand, tumour necrosis factor receptor-1, and potentially other inflammatory markers predict recurrent stroke and other vascular events among patients with a history of small artery ischaemic stroke (85). The aim of the Proteinuria and Albuminuria in Small Subcortical Strokes substudy is to determine the incidence of recurrent stroke in patients with albuminuria compared with patients without albuminuria and to investigate the relationship between renal dysfunction and white matter disease (86).

Discussion

At least 2 00000 S3s occur annually in the United States, with nearly two million survivors at high risk for recurrent stroke and vascular dementia. The condition is even more prevalent in Latin America (4, 5, 8, 87, 88). It remains unclear how to optimally prevent stroke recurrence and cognitive impairment in S3 survivors. Millions of people also have 'subclinical' S3 and cognitive impairment associated with small vessel disease and the results of SPS3 will likely impact their management as well. No secondary stroke prevention study has tested different target levels of blood pressure control in stroke survivors, despite the importance of hypertension as the most common independent risk factor for stroke, particularly for S3. Although S3 is one of the most frequent stroke subtypes among Hispanic people, they have been underrepresented to date in clinical stroke trials.

Identifying effective interventions to prevent or slow the course of cognitive decline is a healthcare priority that SPS3 has been designed to address in patients with cerebral small vessel disease. Lacunar infarct is the most common stroke subtype that predisposes patients to vascular dementia (14, 18, 26), and it is reasonable to speculate that interventions that reduce stroke recurrence will also prevent cognitive decline and vascular dementia in these patients. With detailed cognitive testing at study entry and thereafter annually, the study is designed to assess the effect of antiplatelet therapy and blood pressure management on the rate of cognitive decline. In addition to this important study aim, the imaging data, detailed information on blood pressure and its management over time, and longitudinal measurement of disability and depression will further elucidate the relationships among white matter abnormalities, silent brain infarcts, blood pressure, disability, and mood.

The lack of studies of any type addressing optimal target levels of blood pressure control in hypertensive patients with established cerebrovascular disease led to lengthy discussions during the design phase of the SPS3 blood pressure arm. It was unclear whether the goal of treatment of a hypertensive S3 patient with a systolic blood pressure of 180 mmHg should be to lower by 9mmHg systolic (a concrete interpretation of PROGRESS), to lower to <140 mmHg (per most guideline recommendations), or to seek an even lower blood pressure. The crucial proof-of-principle established by PROGRESS mandated additional trials to define optimal target levels for S3 patients (89).

During SPS3, the management of diabetic participants in the usual SPS3 target (130–149 mmHg) has been a contentious issue. Although not based on the results of randomised-controlled trials, the majority of guidelines recommend systolic blood pressure levels below 130 mmHg (74, 90). The results of several recent studies, however, confirm the appropriateness of the SPS3 design. The results of the ACCORD study did not support the

treatment of hypertension in diabetic patients below the standard target of <140 mmHg systolic for the reduction of the composite outcome of stroke, MI, or vascular death (49). A subgroup analysis of the 6400 participants with diabetes and coronary artery disease from the International SR-Trandolapril Study (INVEST), classified according to their achieved systolic blood pressure, demonstrated no difference in cardiovascular outcomes between the usual control (130–139 mmHg systolic) and the tight control (<130 mmHg systolic) groups (91). Finally, the effect of the 14 mmHg difference in systolic blood pressure between the two groups in the ACCORD study resulted in a 41% reduction in stroke, albeit delayed for one- to two-years. This supports the importance of blood pressure lowering for the primary prevention of stroke in diabetics.

During the design of SPS3 in the early 2000s, the dose of aspirin was carefully considered, and 325 mg daily was selected. The doses of aspirin recommended in guidelines and in clinical use are not based on the results of studies designed to identify the most efficacious dose but rather on a combination of historical precedents and extrapolations from the dosages used in clinical trials, which commonly ranged between 75 and 325 mg daily (55, 92). The results of the Management of Atherothrombosis with Clopidogrel in High-risk patients with TIA or stroke (MATCH) trial, published shortly after the initiation of SPS3, raised concerns about the SPS3 aspirin dose. Serious bleeding was significantly increased among those assigned to the combination of clopidogrel 75 mg plus aspirin 75 mg (93). Blood pressure at entry and control during the trial were not reported for MATCH, whereas blood pressure is carefully controlled in SPS3. Also, MATCH did not require MRIs at entry in contrast to SPS3, where every participant has an MRI study. It is plausible that patients at a high risk of CNS bleed (i.e. prior ICH) are identified based on neuroimaging and not enrolled into SPS3. The unique SPS3 factorial design will allow the risk/benefit of combination antiplatelet therapy to be assessed according to strict blood pressure management.

The notion that the bleeding rate of clopidogrel plus aspirin is dependent on the aspirin dose comes from a nonrandomised exploratory analysis of the CURE trial in which participants were treated with aspirin dosages ranging from 75 to 325 mg daily (94). Participants from Europe given low-dose aspirin had less bleeding than US participants taking higher-dose aspirin with or without clopidogrel. A meta-analysis of placebo-controlled antiplatelet trials failed to show a dose-dependent effect of aspirin on gastrointestinal haemorrhage (95), conflicting with the exploratory results of the CURE trial. Furthermore, two recent analyses, both from the CHARISMA trial, serve to highlight the continuing uncertainty about aspirin dose. Higher doses (100 mg or more) were associated with no clear benefit in those taking aspirin alone and possibly associated with harm when taken in combination with clopidogrel (92). However, an analysis examining thromboxane biosynthesis found that patients receiving lower doses of aspirin (<150 mg daily) had higher concentrations of urinary 11-dehydro thromboxane B2 concentrations, and were found to have associations with an increased risk of serious cardiovascular events (96). Within SPS3, enteric-coated aspirin is used and a gastric protectant is recommended for those patients at a higher risk of bleeding (i.e. elderly or prior gastrointestinal bleed).

Since the launch of SPS3, several large secondary stroke prevention trials testing different antiplatelet regimens have published their results (39, 41, 42, 93). The CHARISMA trial investigated the addition of clopidogrel to aspirin alone, and in their population of patients with established coronary, cerebral, or peripheral arterial disease or with multiple risk factors for atherothrombosis, the distribution of vascular events did not differ significantly between the study groups (534 [6.8%] in the clopidogrel group and 573 [7.3%] in the placebo group, $P = 0.22$). A subgroup analysis compared those with multiple risk factors (asymptomatic) with those with clinically manifest atherothrombosis (symptomatic). Among the patients classified as symptomatic, there was a marginal reduction in the primary end point, whereas among those classified as asymptomatic, the trend favoured the placebo group; an unadjusted test for interaction was borderline significant ($P = 0.045$). While the results of subgroup analyses should always be interpreted with caution, these results do lend support to the design of SPS3, which is examining antiplatelet therapy in a more homogeneous group of patients. Similarly, ACTIVE A showed a large reduction in stroke by dual antiplatelet therapy with clopidogrel plus aspirin vs. aspirin, in a trial restricted to patients with atrial fibrillation. Finally, the PROfESS trial, comparing dipyridamole and aspirin with clopidogrel, did not provide evidence for an antiplatelet regimen that is superior to others in preventing recurrent stroke and major vascular events. To summarise, new trial data appearing since the launch of SPS3 have supported its continuation to address the specific hypothesis in this well-defined stroke subtype.

Limitations of the design

While the underlying vascular disease in most SPS3 participants is small vessel disease, it is not currently possible to define this pathology with certainty. SPS3 excludes those with major cardioembolic sources, with high-grade ipsilateral cervical carotid artery disease, and with prior cortical or large subcortical infarcts on MRI. Hence, while small vessel disease as the cause of stroke is concentrated in the SPS3 cohort, some fraction of participants will have other mechanisms.

Control of blood pressure in SPS3 to reach the target levels does not require the use of specific antihypertensive drugs on the premise that reaching the target is more important than the specific type of antihypertensive agent. If certain pharmacological categories are convincingly shown to have protective effects against stroke in addition to blood pressure-lowering properties and there is unequal use in the two SPS3 treatment arms, interpretation could hypothetically be confounded.

To conclude, SPS3 is the first randomised trial addressing several important clinical and scientific questions relevant to a common ischaemic stroke subtype. As hypertension is the most prevalent and powerful risk factor for S3 and antiplatelet therapy is the standard of care for secondary prevention, definitions of the efficacy and safety of blood pressure control and antiplatelet therapy are tested together. Furthermore, the examination of these interventions in a homogeneous sample of patients with S3, attributed to small vessel disease, will allow a greater precision in the application of the results. The results will inform the management of millions of patients with this common vascular disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig.1.
Overview of entry and follow-up procedures.

Table 1
Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
One of the following lacunar stroke clinical syndromes (adapted from Fisher) lasting >24 h:	Disabling stroke (modified Rankin scale ≥ 4)
Pure motor haemiparesis (PMH)	Previous intracranial haemorrhage (excluding traumatic) or haemorrhagic stroke
Pure sensory stroke	Age under 30 years
Sensorimotor stroke	High risk of bleeding (e.g. recurrent gastro-intestinal or genito-urinary bleeding, active peptic ulcer disease)
Ataxic hemiparesis	Anticipated requirement for long-term use of anticoagulants (e.g. recurrent deep vein thrombosis) or other antiplatelets
Dysarthria-clumsy hand syndrome	Prior cortical or retinal stroke/TIA (diagnosed either clinically or by neuroimaging)
Hemiballism	Prior ipsilateral carotid endarterectomy/stent
PMH with facial sparing	Impaired renal function: glomerular filtration rate <40
PMH with horizontal gaze palsy	Intolerance or contraindications to aspirin or clopidogrel (including thrombocytopenia, prolonged INR)
PMH with contralateral III palsy	Folstein Mini Mental Status Examination score <24 (adjusted for age and education) (97)
PMH with contralateral VI palsy	Medical contraindication to MRI
Cerebellar ataxia with contralateral III palsy	Pregnancy or women of child-bearing potential who are not following an effective method of contraception
Pure dysarthria	Unable or unwilling to provide informed consent
OR Subcortical TIA with positive DWI on MRI	Unlikely to be compliant with therapy/unwilling to return for frequent clinic visits
Absence of signs or symptoms of cortical dysfunction such as aphasia, apraxia, agnosia, agraphia, homonymous visual field defect	Patients concurrently participating in another study with an investigational drug or device
No ipsilateral cervical carotid stenosis ($\geq 50\%$) by a reliable imaging modality, if qualifying event is hemispheric	Other likely specific cause of stroke (e.g. dissection, vasculitis, prothrombotic diathesis, drug abuse)
No major-risk cardioembolic sources requiring anticoagulation or other specific therapy, minor-risk cardioembolic sources will be permitted if anticoagulation is not prescribed	
MRI presence of an S3 (≥ 2.0 cm in diameter) corresponding to the qualifying event (required for all brainstem events) or multiple S3s and absence of cortical stroke and large subcortical stroke (recent or remote).	

Table 2
SPS3 blood pressure measurement protocol

The circumference of the arm is measured at the initial visit in order to select the proper cuff size (bladder of the cuff length >80%; width 40%)
At initial visit, blood pressure measured in each arm three times to select arm for all future measurements. The right arm is the selected arm unless the average SBP in the left arm is at least 10mmHg higher
Blood pressure is measured after holding morning blood pressure medications or after at least 3 h since taking the last dose
Subjects should not have taken caffeine or tobacco within 60min before blood pressure measurement
After 15min of resting quietly, blood pressure is measured in the sitting position with the 'selected' arm relaxed and supported at the heart level
Colin electronic device is used to measure all blood pressures
Physical contact is minimised during measurement
Three blood pressure readings separated by at least two-min in the seated position are recorded. The average of the three readings determines whether patient is within the assigned blood pressure target
One standing measurement is subsequently obtained after standing for two-min
If measured blood pressure is unexpectedly high or low, it will be rechecked using a recently calibrated (preferably mercury) sphygmomanometer

Table 3
Neuropsychological battery

Test (in order of testing)	Domain
Cognitive Assessment Screening Instrument	Global cognition
California Verbal Learning – Immediate	Learning and memory; short recognition
WASI-III Block Design Subtest	Visuo-construction abilities; executive processing speed; planning and problem-solving
WAIS-III Symbol Search Subtest	Visuo-perceptual and motor speed; selective attention
Grooved Pegboard Test	Motor dexterity and speed; visual component
California Verbal Learning – Delayed	Delayed memory
Controlled Oral Word Association	Language abilities; fluency; strategy planning
WAIS-III Digit Span Subtest	Immediate and working memory; sustain attention
Clock Drawing to Command	Executive functioning; visual construction