Predictors of Stroke Recurrence in Patients with Recent Lacunar Stroke and Response to Interventions According to Risk Status: Secondary Prevention of Small Subcortical Strokes Trial

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Background: Among participants in the Secondary Prevention of Small Subcortical Strokes randomized trial, we sought to identify patients with high versus low rates of recurrent ischemic stroke and to assess effects of aggressive blood pressure control and dual antiplatelet therapy according to risk status. *Methods:* Multivariable analyses of 3020 participants with recent magnetic resonance imaging–defined lacunar strokes followed for a mean of 3.7 years with 243 recurrent ischemic strokes. *Results:* Prior symptomatic lacunar stroke or transient ischemic attack (TIA) (hazard ratio [HR] 2.2, 95% confidence interval [CI] 1.6, 2.9), diabetes (HR 2.0, 95% CI 1.5, 2.5), black race (HR 1.7, 95% CI 1.3, 2.3), and male sex (HR 1.5, 95% CI 1.1, 1.9) were each independently predictive of recurrent ischemic stroke. Recurrent ischemic stroke occurred at a rate of 4.3% per year (95% CI 3.4, 5.5) in patients with prior symptomatic lacunar stroke or TIA (15% of the cohort), 3.1% per year (95% CI 2.6, 3.9) in those with more than 1 of the other 3 risk factors (27% of the cohort), and 1.3% per year (95% CI 1.0, 1.7) in those with 0-1 risk factors (58% of the cohort). There were no significant interactions between treatment effects and stroke risk status. *Conclusions:* In this large, carefully followed cohort of patients with recent lacunar stroke and aggressive blood pressure management, prior symptomatic lacunar ischemia, diabetes, black race, and male sex independently predicted ischemic stroke recurrence. The effects of blood pressure targets and dual antiplatelet therapy were similar across the spectrum of independent risk factors and recurrence risk. **Key Words:** Lacunar infarct—cerebral small-vessel disease—prognosis—recurrent stroke.
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Introduction

Small subcortical brain infarcts, commonly known as lacunar strokes, comprise about 25% of ischemic strokes.[1-4] Most result from intrinsic cerebral small artery disease. Independent risk factors for stroke recurrence in patients with lacunar strokes have

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not been well delineated in the existing small studies.[5-8]

The Secondary Prevention of Small Subcortical Strokes (SPS3) randomized trial included 3020 patients with recent magnetic resonance imaging (MRI)–defined lacunar strokes and compared dual antiplatelet therapy with clopidogrel plus aspirin versus aspirin alone and, separately, 2 target goals of systolic blood pressure treatment. Here, independent risk factors for recurrent ischemic stroke in SPS3 participants are identified, and the effects of the 2 treatment interventions are assessed according to the risk of stroke recurrence.[9]

Methods

The rationale, design, participant characteristics, and main results of the SPS3 trial have been reported elsewhere.[10-13] In brief, SPS3 was a randomized, multicenter clinical trial conducted in 82 clinical centers in North America, Latin America, and Spain. Patients of 30 years or older with a recent (≤180 days) symptomatic lacunar stroke who were without surgically amenable ipsilateral carotid artery disease or major-risk cardioembolic sources were eligible and randomized simultaneously in a 2-by-2 factorial design, either to single or dual antiplatelet therapy (double blind) and to 1 of 2 target levels of systolic blood pressure control (<130 mm Hg versus 130-149 mm Hg, open label). Participants with a clinical lacunar syndrome were required to meet MRI criteria that included a diffusion-weighted imaging lesion 2.0 cm or less in size with confirmatory apparent diffusion coefficient image or a well-delineated focal hyperintensity of 2.0 cm or less in size on fluid-attenuated inversion recovery (FLAIR) or T2 that corresponded to the clinical syndrome. In addition, MRI evidence of a recent or remote cortical infarct, large (>1.5 cm) subcortical infarct, or prior intracerebral hemorrhage excluded participation (the presence of microbleeds was not an exclusion). MRI eligibility was determined by local investigators, with images submitted for central interpretation by a neuroradiologist. Salient additional exclusion criteria included disabling stroke (modified Rankin scale score ≥ 4).

Patients with prior lacunar stroke or transient ischemic attack (TIA) required a clinical episode antecedent to the qualifying event that was consistent with a classic subcortical ischemic stroke syndrome and not based solely on neuroimaging findings. Diabetics were those with a history of diabetes mellitus at the time of the qualifying stroke (91%) plus those with diabetes diagnosed at the time of stroke (fasting serum glucose ≥ 120 mg/dL) or initiation of antidiabetic medications during the first 3 months of follow-up (9%). Blood pressure at entry was categorized based on the average of screening systolic blood pressure measurements taken at least 1 week apart, adjusted by adding 5 mm Hg for each antihypertensive medication (up to a maximum of 4) at the time of the measurement. Normotensive was defined as less than 120 mm Hg, prehypertensive as 120 to less than 140 mm Hg, stage I hypertension as 140 to less than 160 mm Hg, and stage II hypertension as 160 mm Hg or more.

These analyses focused on the risk of recurrent *ischemic* stroke, in contrast to the primary outcome of the SPS3 trials, which also included intracranial hemorrhage (12% of primary events).[12,13] Recurrent ischemic stroke was clinically defined as a focal neurological deficit of sudden onset persisting for greater than 24 hours with hemorrhage excluded by acute neuroimaging. All strokes were reviewed by a central adjudication committee that was unaware of treatment assignment and that additionally classified ischemic strokes by presumed mechanism based on available diagnostic studies. The antiplatelet trial was terminated 4 months before the blood pressure trial.[12,13] Here, all ischemic strokes during follow-up in the blood pressure trial are considered.[13] For the analyses of predictors of ischemic stroke, the 238 (98%) recurrent ischemic strokes were combined with 5 (2%) strokes thought to be ischemic but lacking neuroimaging. Recurrent lacunar infarcts (n = 136) comprised 56% of ischemic strokes, and independent predictors of this subgroup are separately assessed.

Patient characteristics selected for inclusion in the analysis were the clinical characteristics reported in a previously published description of participant features[12] plus body mass index, stage of hypertension, and estimated glomerular filtration rate.[14] To identify patient characteristics independently predictive of ischemic stroke, the cohort was randomly divided into 2 groups of equal size, that is, derivation and validation cohorts. Clinical features independently associated with ischemic stroke were identified in the derivation cohort using forward stepwise Cox proportional hazards modeling techniques (likelihood ratio test), both without and with stratification by assigned treatment groups to confirm that treatment assignment did not influence identification of predictors. Independent factors were then combined by inspection in the derivation cohort to yield a risk stratification scheme that was then applied to the validation cohort. Cumulative recurrent stroke rates were compared across risk strata by fitting a Kaplan–Meier curve (log rank test). Annualized stroke rates were calculated with person-years as the denominator with 95% confidence intervals (CIs) computed assuming the Poisson distribution. Absolute differences and CIs in stroke rates between groups were also computed assuming the Poisson distribution. All analyses followed an intention-to-treat paradigm. All tests were 2 sided, and statistical significance was accepted at the .05 level, with no adjustment made for multiple comparisons. Analyses were performed with SPSS version 20.

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