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Frequency, Risk Factors, and Outcome of Coexistent Small Vessel Disease and Intracranial Arterial Stenosis Results From the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) Trial

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Importance Intracranial arterial stenosis (ICAS) and small vessel disease (SVD) may coexist. There are limited data on the frequency and risk factors for coexistent SVD and the effect of SVD on stroke recurrence in patients receiving medical treatment for ICAS.

Objective To investigate the frequency and risk factors for SVD and the effect of SVD on stroke recurrence in patients with ICAS.

Design, Setting, and Participants A post hoc analysis of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study, a prospective, multicenter clinical trial. Among 451 participants, 313 (69.4%) had baseline brain magnetic resonance imaging scans read centrally for SVD that was defined by any of the following: old lacunar infarction, grade 2 to 3 on the Fazekas scale (for high-grade white matter hyperintensities), or microbleeds. Patient enrollment in SAMMPRIS began November 25, 2008, and follow-up ended on April 30, 2013. Data analysis for the present study was performed from May 13, 2014, to July 29, 2015.

Main Outcomes and Measures Risk factors in patients with vs without SVD and the association between SVD and other baseline risk factors with any ischemic stroke and ischemic stroke in the territory of the stenotic artery determined using proportional hazards regression.

Results Of 313 patients, 155 individuals (49.5%) had SVD noted on baseline magnetic resonance imaging. Variables that were significantly higher in patients with SVD, reported as mean (SD), included age, 63.5 (10.5) years (P < .001), systolic blood pressure, 149 (22) mm Hg (P < .001), glucose level, 130 (50) mg/dL (P = .03), and lower Montreal Cognitive Assessment scores (median, 24 [interquartile range, 20-26]; P = .02). Other significant variables were the number of patients with diabetes mellitus (88 of 155 [56.8%]; P = .003), coronary artery disease (46 [29.7%]; P = .004), stroke before the qualifying event (59 [38.1%]; P < .001), old infarct in the territory of the stenotic intracranial artery (88 [56.8%]; P < .001), and receiving antithrombotic therapy at the time of the qualifying event (109 [70.3%]; P = .005). The association between SVD and any ischemic stroke was nearly significant in the direction of a higher risk (18 [23.7%]; P = .07) for patients with SVD. On bivariate analysis, SVD was not associated with an increased risk on multivariable analyses (hazard ratio, 1.7 [95% CI, 0.8-3.8]; P = .20). In addition, SVD was not associated with an increased risk of stroke in the territory on either bivariate or multivariable analyses.

Conclusions and Relevance Although SVD is common in patients with ICAS, the presence of SVD on baseline magnetic resonance imaging is not independently associated with an increased risk of stroke in patients with ICAS.

Trial Registration clinicaltrials.gov Identifier NCT00576693

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Atherosclerosis of the large intracranial arteries is a common cause of stroke that is associated with a high risk of recurrent stroke. Intracranial arterial stenosis (ICAS) may coexist with disease in the small perforator vessels (termed small vessel disease [SVD]) that arise from the large basal arteries of the brain or their branches. The presence of SVD is inferred from the presence of prominent white matter hyperintensities, old lacunar infarcts, or cerebral microbleeds observed on brain imaging, which are strongly linked to each other and have been associated with a higher risk of stroke recurrence and cognitive decline.

Although some studies have suggested that patients with ICAS may be particularly prone to having coexistent SVD, there are limited data on the frequency and risk factors for coexistent SVD and the effect of SVD on stroke recurrence in patients with ICAS who receive medical treatment. The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial provided a unique opportunity to investigate these associations.

**Methods**

**Study Population and Design**

SAMMPRIS was a prospective, multicenter clinical trial funded by the National Institute of Neurological Disorders and Stroke. Enrollment began on November 25, 2008, and follow-up was completed on April 30, 2013. Data analysis for the present study was performed from May 13, 2014, to July 9, 2015. Participants included 451 patients with symptomatic ICAS randomized to aggressive medical management and percutaneous transluminal angioplasty and stenting or aggressive medical management alone. Details of the trial’s design and results of the comparison between medical management and percutaneous transluminal angioplasty and stenting or aggressive medical management alone. Details of the trial’s design and results of the comparison between medical management and percutaneous transluminal angioplasty and stenting have been published.

Eligible patients were aged 30 to 80 years and had experienced nondisabling stroke or transient ischemic attack within 30 days before enrollment attributable to angiographically proved 70% to 99% stenosis of a major intracranial artery. The Medical University of South Carolina institutional review board approved the present study. All patients provided written informed consent. Participants did not receive financial reimbursement.

All patients enrolled in SAMMPRIS were required to undergo baseline brain imaging that was reviewed centrally by a neuroradiologist (Z.R.). Because magnetic resonance imaging (MRI) of the brain is far more sensitive for diagnosing SVD compared with computed tomography of the brain, we excluded 138 patients who had baseline computed tomography alone or inadequate baseline MRI, leaving 313 patients (69.4%) for the present analysis.

**Definition of SVD**

All white matter hyperintensities and subcortical infarcts on T2 or fluid-attenuated inversion recovery and lesions with low signal intensity on T2* gradient-echo images were evaluated by the SAMMPRIS central neuroradiology reader (Z.R.) to determine the presence of SVD, which was defined by the presence of any of the following: grade 2 to 3 for white matter hyperintensities on the Fazekas scale, old lacunar infarct, or cerebral microbleed (≥1). The boundaries of white matter hyperintensities and old lacunar infarcts were differentiated from acute ischemic lesions by visually coregistering fluid-attenuated inversion recovery images with diffusion-weighted images. Supratentorial lacunar infarcts were defined as subcortical infarcts that were 1.5 cm or less in the territory of perforator branches to the basal ganglia, thalamus, internal capsule, corona radiata, or centrum semi-ovale that had central signal intensity corresponding to the cerebrospinal fluid with a peripheral hyperintense rim on fluid-attenuated inversion recovery images.

Infratentorial lacunar infarcts were defined as infarcts that were a size of 1.5 cm or less and found in the territory of perforator branches to the brainstem or cerebellum. Cerebral microbleeds were defined as focal, round, very low-signal-intensity lesions (areas of signal loss) on gradient-echo imaging with a diameter of less than 10 mm.

**Statistical Analysis**

We compared baseline risk factors between patients with vs without SVD for all patients enrolled in the trial (ie, both the percutaneous transluminal angioplasty and stenting and medical treatment groups) using the Fisher exact test (for percentages), independent-groups t test (for means), or Wilcoxon rank sum test (for medians). Among patients in the medical group, we evaluated the bivariate association of SVD and each of the other baseline risk factors with any ischemic stroke and with ischemic stroke in the territory of the stenotic artery using proportional hazards regression. To assess the effect of potential confounding factors on the association between SVD and each of the outcomes, we identified the baseline risk factors that were different between patients with and those without SVD (as described above) and also associated with each of the outcomes as selected using multivariable proportional hazards regression with the backward elimination method. Candidate risk factors for multivariable analysis were those with P < .10 in the bivariate analyses described above. After the confounding risk factors were identified for each outcome, we estimated the adjusted hazard ratio for SVD using a proportional hazards regression model that included SVD and the confounding risk factors. Patients lost to follow-up and those who withdrew consent were censored at the last contact date. All reported P values are 2-sided and P < .05 was considered statistically significant. All analyses were performed from May 13, 2014, to July 29, 2015, using SAS, version 9.3 (SAS Institute Inc).

**Results**

**Frequency and Risk Factors for SVD in Both Groups**

Of the 313 patients in this analysis, 155 individuals (49.5%) had evidence of SVD on baseline brain MRI. Among these, 76 patients (49.0%) showed white matter hyperintensities of Fazekas grade 2 to 3 (isolated in 27 patients, with a lacune in 42, microbleeds in 4, and a lacune and microbleeds in 3); 121 patients (78.1%) had an old lacune (isolated in 72, with a microbleed alone in 4); and 14 patients (9.0%) had microbleeds (isolated in 3).
Demographics and baseline clinical features of participants with and without SVD are provided in Table 1. Variables that were significantly higher in patients with SVD, reported as mean (SD), included age, 63.5 (10.5) years ($P < .001$), systolic blood pressure, 149 (22) mm Hg ($P < .001$), glucose level, 130 (50) mg/dL ($P = .03$) (to convert to millimoles per liter, multiply by 0.0555), and lower Montreal Cognitive Assessment (MoCA) scores (median, 24 [interquartile range, 20-26]; $P = .02$). Other significant variables were the number of patients with diabetes mellitus (88 [56.8%]; $P = .003$), coronary artery disease (46 [29.7%]; $P = .004$), stroke before qualifying event (59 [38.1%]; $P < .001$), old infarct in the territory of the stenotic intracranial artery (88 [56.8%]; $P < .001$), and receiving antithrombotic therapy at the time of qualifying event (109 [70.3%]; $P = .005$).

**Stroke Outcomes in Patients With and Without SVD in the Medical Group**

Table 2 reports the rates of all ischemic stroke and stroke in the territory of the stenotic artery in patients with and with-
out SVD at 30 days, 1 year, and 2 years in the medical group of SAMMPRIS. The association between SVD and any ischemic stroke was nearly statistically significant ($P = .03$) in the direction of a higher risk for patients with SVD, but there was no significant difference between patients with and without SVD for stroke in the territory ($P = .16$).

Only 1 of 227 patients (0.4%) in the medical group of SAMMPRIS had an intracerebral hemorrhage (ICH) during follow-up; this patient had lacunar infarcts in the right caudate territory of the stenotic artery.

Baseline factors at a level of $P < .10$ for any ischemic stroke on bivariate analyses included SVD, female sex, hypertension, diabetes mellitus, not receiving a statin at enrollment, physical activity out of target range at enrollment (target was ≥30 minutes of moderate exercise at least 3 times per week), elevated high-density lipoprotein cholesterol and glucose levels, low MoCA score, stroke (rather than transient ischemic attack) as the qualifying event for the trial, old infarct in the territory of the stenotic artery on baseline brain imaging, and modified Rankin scale score of 1 or higher (eTable 1 in the Supplement). Among these factors, after excluding SVD, the only factors independently associated with ischemic stroke in the territory during follow-up were not receiving statin therapy at enrollment, old infarct in the territory of the stenotic artery, and modified Rankin scale score of 1 or higher (Table 5). Small vessel disease was not associated with ischemic stroke in the territory of the stenotic artery on baseline brain imaging on either bivariate analysis ($P = .16$) or multivariable analysis ($P = .63$) after adjusting for old infarct in the territory of the stenotic artery, which was the only baseline feature that was both different between patients with and without SVD and also associated with ischemic stroke in the territory of the stenotic artery.

### Discussion

To our knowledge, SAMMPRIS provides the largest cohort yet to study the frequency and risk factors of coexistent SVD in patients with ICAS. This analysis shows that SVD as defined by brain imaging features occurs in 50% of patients with recently symptomatic, high-grade ICAS and is associated with the typical risk factors associated with SVD: older age, diabetes, and poorly controlled blood pressure.8,31
The higher frequency of previous stroke and coronary disease in patients with SVD in SAMMPRIS is likely explained by the higher burden of risk factors in these patients. Those with previous stroke or coronary disease would typically receive antithrombotic therapy, which likely explains the higher use of antithrombotic agents at the time of the qualifying transient ischemic attack or stroke in SAMMPRIS participants with SVD (Table 1). The association of SVD and cognitive impairment is well established, and is likely the explanation for the significantly lower MoCA scores at baseline in patients with SVD compared with patients without SVD (Table 1).

Although the observed rates of any ischemic stroke in patients with SVD vs those without SVD in the medical group in SAMMPRIS (Table 2) suggest that patients with SVD may be at higher risk of any ischemic stroke, the multivariable analyses indicated that SVD is not independently associated with any ischemic stroke (Table 4). This implies that the numerically higher stroke rate in patients with SVD (Table 2) is associated with other baseline features with which SVD is associated (eg, diabetes and low MoCA score) (Table 4). These findings are distinct from previous studies that have indicated that white matter hyperintensities or silent lacunar infarcts are associated with an increased risk of stroke even after controlling for vascular risk factors.

The association between diabetes and increased risk of stroke is well established, but the explanation for the association between low MoCA score and increased risk of any ischemic stroke in the medical group in SAMMPRIS is less apparent. It is possible that this association may be explained by a higher cumulative burden of stroke risk factors in patients with a low MoCA score or that a low MoCA score may be a marker of severe underlying pathologic changes in the penetrating arteries that could have increased the risk of stroke, particularly lacunar stroke, in patients receiving medical treatment in SAMMPRIS.

Although a low MoCA score was associated with an increased risk of any ischemic stroke during follow-up, it was not associated with an increased risk of stroke in the territory of the stenotic artery (eTable 2 in the Supplement). This difference may be explained by the relative frequency of lacunar infarction caused by SVD during follow-up in compared with out of the territory of the stenotic artery, that is, the frequency of lacunar infarction in the territory of the stenotic artery from coincidental SVD (even if more severe when associated with low MoCA scores) is low compared with the more common mechanisms of stroke from ICAS (ie, artery-to-artery embolism and hypoperfusion).

It is likely that a high proportion of strokes outside of the territory of the stenotic artery during follow-up in SAMMPRIS patients who were prescreened for a known cardioembolic source and other vascular disorders were caused by lacunar infarctions from SVD.

Previous studies have suggested that patients with leukoariosis and microbleeds are at increased risk of ICH. However, in both SAMMPRIS and the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, the frequency of ICH in patients receiving medical treatment was low despite the high frequency of SVD in patients with ICAS and the use of combination aspirin and clopidogrel for 90 days followed by aspirin alone in SAMMPRIS and the use of warfarin in one of the arms of the WASID trial. It is likely that the effective blood pressure–lowering protocol used in SAMMPRIS contributed to the low rate of ICH in the medical arm of the trial. However, blood pressure control was not nearly as effective in WASID and yet those patients also had a low rate of ICH (only 2 of 289 patients receiving warfarin had an ICH during a mean follow-up of 1.8 years).

The strengths of our study are that the data were derived from a large, prospective, multicenter study; systematic MRI-based assessment of SVD was used; and the protocol was driven by follow-up and adjudication of events. The major weaknesses are the post hoc analysis, the possibility that some patients with isolated lacunar infarcts who were defined as having SVD may have had an alternative cause of the lacunar infarct (eg, branch artery atherosclerosis at the site of the ICAS), and the limited statistical power despite the fact that this is the largest cohort of patients described with coexistent SVD and ICAS.

Conclusions

Patients with recent symptoms of severe ICAS have a high frequency of SVD based on brain imaging features. Patients with ICAS who are at particularly high risk of coexistent SVD...
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Author Contributions: Drs Kwon and Chimowitz had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kwon, Lynn, Turun, Derdeyn, Fiorella, Janis, Rumboldt, Chimowitz. Acquisition, analysis, or interpretation of data: Kwon, Lynn, Turun, Derdeyn, Fiorella, Janis, Rumboldt. Chimowitz. Drafting of the manuscript: Kwon, Lynn. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Kwon, Lynn. Obtained funding: Lynn, Turun, Chimowitz. Administrative, technical, or material support: Kwon, Lynn, Derdeyn, Montgomery. Study supervision: Kwon, Lynn, Turun, Janis, Chimowitz.

Conflict of Interest Disclosures: Mr Lynn reported receiving grants from the National Institute of Neurological Disorders and Stroke (NINDS) during the study. Dr Turun reported receiving a $23,000 grant from the National Institutes of Health (NIH)/NINDS unrelated to this project and personal fees from Gore and Boehringer ingelheim for participating as a stroke adjudicator in clinical trials unrelated to this work. Dr Derdeyn reported having relationships with companies that manufacture medical devices for the treatment of cerebrovascular disease in general, although none directly involved in this study, including W. L. Gore and Associates (scientific advisory board consultant), Microvention, Inc (Angiographic Core Laboratory for clinical trial), Penumbra, Inc (Data Safety Monitoring Board member for clinical trial), and Pulse Therapeutics (chair, Scientific Advisory Board). Dr Fiorella reported receiving institutional payment for research/salary support from Microvention, ScienT, and Siemens; consulting fees from Cordis and Cordiven Ev3; royalties from Codman & Shurtleff (REVIVE); and having ownership and stock interests in CSVL, TDC Technologies, and Vascular Simulators LLC. Dr Rumboldt reported receiving research support from Bayer unrelated to this study and being a speaker/consultant for Braico Diagnostics, not related to this project. Dr Chimowitz reported receiving a grant from NIH/NINDS related to this study, as well as other grants from NIH/NINDS and personal fees from Gore Associates, Medtronic, and Merck/Parexel for participating as a stroke adjudicator or data safety monitoring board member on clinical trials unrelated to this work. He also reported receiving personal fees as an expert witness in medical legal cases related to stroke. No other disclosures were reported.

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