Interventional and New Approaches to Stroke Prevention

Intracranial Stenting
SAMMPRIS

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Current Status
The Stenting and Aggressive Medical management for the Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial established aggressive medical management as superior to angioplasty and stenting for symptomatic intracranial atherosclerotic disease. This presentation addresses some criticisms of the trial, emphasizes key knowledge gained from the study and proposes potential new directions for research in this area. At present, the data from the trial are limited to complete 30-day outcomes for all enrolled patients and follow-up to 1 year in approximately half of the cohort.1 Enrollment was stopped early at the recommendation of the Data and Safety Monitoring Board because of higher than expected 30-day complication rates in the stenting arm and a futility analysis indicating essentially no chance that stenting would be proven superior. A total of 451 patients (59% of the target) had been enrolled, with 227 randomized to aggressive medical management alone and 224 to aggressive medical management plus stenting. Follow-up was completed in March 2013 and study close-out is underway. Presentation of the final primary results is planned for the Fall of 2013.

Primary Outcome
The 30-day rate of stroke and death was 14.7% in the percutaneous transluminal angioplasty and stenting group (12.5% nonfatal stroke, 2.2% fatal stroke) and 5.8% in the medical group (5.3% nonfatal stroke, 0.4% nonstroke death; \( P = 0.002 \)). Beyond 30 days, stroke in the same territory occurred in 13 patients in each group. These events were predefined primary end points and were blindly adjudicated. Mean duration of follow-up at the time of this analysis was 11.9 months. The Kaplan–Meier curves were significantly different (\( P = 0.009 \)) and yield 1-year rates of the primary end point of 20.0% in the percutaneous transluminal angioplasty and stenting group and 12.2% in the medical group. We concluded that aggressive medical management was superior to angioplasty and stenting for patients with symptomatic intracranial atherosclerotic disease. Because of the clinical importance and conclusive nature of the early data, these results were published in 2011. As noted above, follow-up of enrolled patients continues, and some changes in the long-term rates of stroke in both groups are possible.

Common Questions
Three issues have been raised at meetings or published critiques: the patient population chosen for the trial, the medical regimen, and the impact of operator experience on the 30-day outcomes in the trial.2,3 One of these published critiques have had responses from the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) investigators.4,5

Was This the Right Patient Population?
Yes. The best (prospective, longitudinal, and adjudicated outcomes) definition of a high-risk group was provided by the Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) trial.6 This was a randomized trial of warfarin versus aspirin for patients with 50% to 99% atherosclerotic stenosis of a major (ie, amenable to angioplasty and stenting) intracranial artery: the internal carotid, M1 segment of middle cerebral artery, vertebral and basilar arteries. Patients were required to have had recent (within 90 days) ischemic symptoms to qualify for enrollment. Kasner et al7 performed a prespecified analysis to identify high-risk subgroups. Patients with 70% to 99% stenosis and transient ischemic attack or stroke within 30 days before enrollment had the highest rate of ischemic stroke in the territory of the symptomatic artery: 22.9% at 1 year (95% confidence interval, 15.4%–30.4%), 25.0% at 2 years (95% confidence interval, 17.2%–32.9%). SAMMPRIS was designed using risk estimates from this latter group. The likelihood that angioplasty and stenting would be beneficial in patients without these high-risk features was considered low.

These prospective data from WASID laid to rest a number of hypotheses generated from previous retrospective studies: posterior circulation stenosis was not a higher risk disease.
than anterior circulation,\textsuperscript{9} posterior circulation stenosis did not respond better to warfarin than aspirin,\textsuperscript{9} and patients already on antithrombotic medication were not at higher risk for stroke.\textsuperscript{10} Patients in WASID who had their qualifying event on an antithrombotic agent were at no higher risk for a recurrent event than those on no treatment at the time of their qualifying event.\textsuperscript{11} SAMMPRIS results to date have also not found any relationship between failure of antithrombotic therapy and higher risk of recurrent stroke either (Lutsep et al 2012 International Stroke Conference oral abstract).

Was the SAMMPRIS Medical Regimen Real World?
The medical regimen in SAMMPRIS was carefully developed on the basis of the data from WASID, national guideline recommendations for risk factor control, results from recent stroke prevention trials, and the need to balance antiplatelet medication between the stenting and the medical groups. In WASID, patients with poorly controlled blood pressure or elevated low-density lipoprotein during follow-up had a significantly higher rate of stroke, vascular death, or myocardial infarction compared with patients with good control of these risk factors.\textsuperscript{12} Blood pressure (systolic <140 in patients with non–diabetes mellitus and <130 in patients with diabetes mellitus) and low-density lipoprotein (<70 mg/dL) targets were developed using The Seventh Report of the Joint National Commision on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) and The National Cholesterol Education Program Adult Treatment Panel III (NCEP-III) guidelines, respectively.\textsuperscript{13,14} The benefit of low-density lipoprotein and hypertension control for stroke risk reduction is well established.\textsuperscript{15–17} Dual antiplatelet therapy for the first 90 days, followed by aspirin, was justified by the need for dual antiplatelets after stenting, plus some evidence of potential benefit for dual antiplatelet treatment if given within 30 days of ischemic symptoms.\textsuperscript{18,19} In addition, it is likely that the pathophysiology of recurrent stroke related to recently symptomatic intracranial large artery atherosclerosis is similar to that of myocardial infarction related to recently symptomatic coronary atherosclerosis, which is more effectively treated with aspirin and clopidogrel than aspirin alone.\textsuperscript{20}

Risk factor management at each site was managed by a team, including the site neurologist, a study coordinator, and a lifestyle coach (from INTERxVENT, Columbus, OH).\textsuperscript{21} Patients were seen at enrollment, at 30 days, and then every 4 months after enrollment. If blood pressure was not within target, adjustments in medical treatment were made and the patient returned in 30 days for a check. The protocol for achievement of these targets was supervised by the study neurologist. A lifestyle coach was used to assist in weight loss and smoking cessation, but this intervention typically started 30 days after enrollment and cannot account for the much lower than expected 30-day rates in the medical arm.

Were the High Procedural Complication Rates Related to Poor Performance?
Interventionists credentialed with less Wingspan experience were not responsible for the high rate of periprocedural stroke in SAMMPRIS.\textsuperscript{22} The interventionists were selected by a committee of experienced interventionists on the basis of the documentation of experience with intracranial angioplasty and stenting.\textsuperscript{23} Interventionists with higher numbers (>10) of Wingspan cases submitted for credentialing tended to have higher rates of 30-day events (19.0% versus 9.9%) than those with <10 cases. High enrolling sites in the trial tended to have lower rates of hemorrhagic stroke (9.8% at sites enrolling <12 patients versus 2.7% at sites enrolling ≥12 patients). This may reflect issues related to protocol adherence and blood pressure control after stenting. It is also important to note that the outcome of the study was overwhelmingly positive for medical therapy and that the stroke rates after 30 days were similar between the 2 groups. If the 30-day rate of the primary end point in the stenting arm could be lowered substantially (even as low as the 30-day rate in the medical arm of 5.8%), it does not seem that stenting could offer any significant advantage over aggressive medical therapy in this patient population on the basis of the current follow-up data from the trial.

What Have We Learned from SAMMPRIS?
Beyond the primary outcome, there are several very important results from this trial. First, the 30-day and 1-year risk of stroke in the medical arm was dramatically lower than expected on the basis of the estimates from WASID. This very likely reflects a therapeutic benefit from the SAMMPRIS medical regimen in this patient population. Whether this is related to one or all the medical interventions (dual antiplatelet agents for 90 days, antihypertensive, and statin therapy) is not known at this point but may become clearer when analyses relating risk factor control and outcome are done.

Second, the types and frequency of some complications from stenting were unexpected. Of the 213 patients randomized to the stenting arm who underwent stenting (n=208) or angioplasty alone (n=5), 13 had hemorrhagic strokes: 7 were parenchymal hematomas remote from the stented vessel segment and 6 were subarachnoid hemorrhage. Most of the subarachnoid hemorrhage was attributable to wire perforation. The nature of the parenchymal hemorrhages is uncertain, but because most were delayed by hours after the procedure, reperfusion hemorrhage is the most likely cause. Statistical analysis (univariate followed by stepwise logistic regression) identified an association of higher degrees of stenosis and preoperative clopidogrel loading (600 mg) in combination with high procedural activated clotting time (>300 seconds) with parenchymal hemorrhage.\textsuperscript{24}

The majority of the 19 periprocedural ischemic strokes in stented patients were local perforator occlusions, and most of these were in the basilar artery Multivariate analysis found an association of nonsmoking, basilar location, older age, and diabetes mellitus with a higher risk of periprocedural ischemic stroke. The smokers paradox has also been observed in studies of coronary intervention and may relate to confounding risk factor variables and the possible interaction between smoking and clopidogrel responsiveness.\textsuperscript{24}

Future Directions
Given these results, future areas for research in this population include the identification of subgroups at a high risk of stroke despite aggressive medical therapy. If safer and more effective
endovascular procedures can be developed, further trials will be needed to determine if these procedures lower the risk of stroke compared with aggressive medical therapy in these high-risk subgroups. In addition, the identification of clinical, imaging, or technical factors predisposing to parenchymal hemorrhage or perforator infarction after angioplasty and stenting will be important.

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Disclosures

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References

20. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with


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