Is There a Future for Endovascular Treatment of Intracranial Atherosclerotic Disease After Stenting and Aggressive Medical Management for Preventing Recurrent Stroke and Intracranial Stenosis (SAMMPRIS)?

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The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke and Intracranial Stenosis (SAMMPRIS) trial, a randomized clinical trial comparing aggressive medical management to stenting with aggressive medical management for symptomatic intracranial stenosis, was prematurely halted when a high rate of periprocedural events was found in the stent arm. The trial also demonstrated a high rate of stroke with medical management. This article explores possible reasons for these outcomes and discusses some weaknesses of the trial. Against this background endovascular therapy should continue to be explored in the treatment of this disease. (Stroke. 2012;43:580-584.)

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The initial results of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke and Intracranial Stenosis (SAMMPRIS) trial raises a question regarding the role of endovascular therapy in the management of symptomatic intracranial atherosclerotic disease. SAMMPRIS randomized patients with symptomatic intracranial stenosis (≥70%) to aggressive medical management versus endovascular therapy with aggressive medical management. Enrollment in the SAMMPRIS Trial was halted after 451 patients underwent randomization because the 30-day stroke and death rate in the group receiving endovascular therapy and medical management was 14.7% versus 5.8% in the group receiving medical management alone. In addition, the probability of experiencing the primary end point (any stroke or death within 30 days after enrollment or after any revascularization procedure of a qualifying lesion or a stroke in the territory of the symptomatic artery beyond 30 days) at 1 year was 20% in the endovascular therapy group and 12.2% in the medical management group.1

The trial publication implicates 2 reasons for the disparity between the medical therapy group and the endovascular therapy group. First, the medical management arm had markedly lower rates of stroke than those seen in the preceding Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) trial. Second, the 30-day stroke or death rate in the endovascular group was much higher than previously reported with the use of the trial device. Despite these findings, there are several questions regarding the trial, its application to clinical practice, and the continued use of endovascular therapy in these patients.

The endovascular arm of the SAMMPRIS trial was conducted with a single device system: the Gateway angioplasty balloon and Wingspan stent. This first-generation device is the only device currently approved for treatment of symptomatic intracranial stenosis. Was this device ready for this trial? The Wingspan received US Food and Drug Administration approval under a humanitarian device exemption application in August 2005. The SAMMPRIS study protocol was first received by the National Institutes of Health in December 2007 and the study began in October 2008. What was known about the performance and safety of this first-generation device before the start of the study?

A publication by Bose et al highlighted the results of a small 45-patient study, which led to limited Food and Drug Administration approval. This study reported a 30-day ipsilateral stroke and death rate of 4.5%; at 6-month follow-up, the ipsilateral stroke and death rate was 7%. However, this study evaluated patients with ≥50% stenosis (mean percent stenosis was 74.9%). Periprocedural results with the Wingspan stent were also reported by Fiorella et al as part of a US multicenter registry conducted by many of the physicians who participated in SAMMPRIS. Seventy-eight patients with 82 lesions with pretreatment stenosis of ≥50% (mean percent stenosis was 74.6±13.9%) were treated. There were 5 major periprocedural complications (6.4% complications on a per-patient basis) with 4 resulting in death. In addition, one patient had visual symptoms lasting >24 hours, 5 patients had extracranial dissections, and 13 of 38 patients...
(34.2%) who had diffusion-weighted imaging within 72 hours after the procedure had new infarcts. Zaidat et al reported the only periprocedural results on patients that matched the SAMMPRIS trial inclusion criteria of ≥70% symptomatic intracranial stenosis. One hundred twenty-nine patients were included in this National Institutes of Health registry report organized by the SAMMPRIS investigators. The mean stenosis in this group was 82%±9%. This study showed a high rate of periprocedural complications with 12 strokes and deaths (9.6%) reported in the first 30 days. Other complications included 4 cases of stent thrombosis, 2 patients with infarctions on MRI and neurological signs lasting <24 hours, 1 patient with somnolence for 3 days, and 2 with vessel dissections.

Beyond the 30-day periprocedural period, what information was available regarding the stroke rate in the territory of the treated artery? Three publications from the US Multi-Center Registry highlighted aspects of the restenosis rate seen with the Wingspan stent. The first of these reported a series of 78 patients with 84 lesions for whom imaging follow-up was available (average duration of follow-up was 5.9 months). In this group, 25 patients (32.0% on a per-patient basis) had in-stent restenosis. Four additional patients (5.1%) had complete thrombosis of the stented vessel. Eight of these 29 patients were symptomatic (4 with strokes and 4 with transient ischemic attacks). A subsequent publication highlighted 93 treated lesions (results reported on a per-lesion basis). Of the 93 lesions, 29 (32.2%) developed in-stent stenosis. Five additional lesions were completely thrombosed and not reported as part of this follow-up, making it impossible to determine if in-stent restenosis preceded thrombosis. Nine (9.7%) lesions reported were symptomatic. This group’s final publication reported that 36 of 129 (27.9%) patients with imaging follow-up experienced in-stent restenosis. Thirteen were symptomatic (9 having transient ischemic attacks and 4 ipsilateral strokes). Although these publications documented a relatively high rate of in-stent restenosis with the Wingspan stent, they were limited reports of patients with imaging follow-up and did not communicate the periprocedural stroke and death rate for all treated patients.

The only study that reported the stroke or death rate within 30 days or stroke in the territory of stenting beyond 30 days was the National Institutes of Health registry study. The authors concluded that the data from the registry when compared with high-risk patients from the WASID trial “do not rule out either that stenting could be associated with a substantial relative risk reduction (eg, 50%) or has no advantage compared with medical therapy.” The study reported results in 129 patients. There were 12 strokes or deaths within the 30-day period and 4 additional strokes in the territory of the stented artery between 30 days and 6 months. Therefore, the rate of any stroke or death within 30 days and stroke in the territory in the stented artery beyond 30 days (up to 6 months) was 14%. This 14% rate is remarkably similar to the rate of ipsilateral stroke seen at 6 months in the subgroup of patients with ≥70% stenosis in the WASID study. In other words, the Wingspan stented patients (who had the benefit of both aspirin and Plavix) did not seem to have a benefit at 6 months when compared with the WASID patients (receiving either aspirin or warfarin alone). The US Multi-Center Registry published this year (2 months after the SAMMPRIS trial ended) reported the combined 30-day death and stroke rate and the longer-term ipsilateral stroke rate. They treated 158 patients with 143 having at least 3 months follow-up and 110 having 12-month follow-up. In this group with a mean follow-up of 14.2 months, there were 13 patients who had ipsilateral strokes beyond the 30-day periprocedural period. The majority of these strokes (10 of 13 [76.9%]) occurred within 6 months of treatment. In those patients with ≥70% stenosis, 13.9% met the primary end point of any stroke or death within 30 days and stroke in the territory in the stented artery beyond 30 days (a number also remarkably similar to the WASID study).

The high rate of stroke in the endovascular arm of the study was not attributed by the SAMMPRIS investigators to inexperience. They argued that the trial interventionalists were credentialed to participate on the basis of their experience; the rates of periprocedural stroke did not decline over the course of enrollment and were not significantly different between high and low enrolling sites. Trial interventionalists were required to submit results of their most recent 20 consecutive intracranial stent or angioplasty cases. The operator must have performed a minimum of 3 Wingspan cases. Additional experience could come from the use of other intracranial stents for atherosclerosis, self-expanding stents for aneurysm treatment, or from angioplasty alone.

The SAMMPRIS investigators reached a quite different conclusion regarding inexperience with the earlier publication of the National Institutes of Health registry data. In this publication, significant differences were found between the high and low enrolling sites for stroke or death within 30 days and for stroke in the territory of the treated artery after 30 days. The authors pointed out that although the rate of any stroke or death within 30 days or stroke in the territory beyond 30 days was 14% at 6 months for the entire group, it was 9% at high enrolling sites versus 23% at low enrolling sites, suggesting with greater experience the primary outcome measure would decrease in stented patients.

If we accept the current case made by the SAMMPRIS investigators that higher rates of stroke and death do not reflect inexperience and do not decline over time, this suggests that there is an inherently high risk to the procedures with the device used in the trial, which does not decline with user experience. Are there design considerations that would possibly affect the safety profile of this first-generation device? The use of this system requires a 2-step procedure involving angioplasty followed by removal of the angioplasty microcatheter, maintenance of an exchange wire across the stenosis, and placement of a self-expanding stent. The Wingspan Stent System requires a 6-Fr guide catheter rather than a 5-Fr system. In addition, it was not designed as a rapid exchange system. It requires a long (300-cm) exchange length wire be left intracranially, whereas the full length of the angioplasty catheter is removed and the full length of the stent delivery catheter is placed. This system design has a number of characteristics that could lead to increased complications. The necessitated use of a larger guide may be
problematic in smaller extracranial vessels, particularly in the posterior circulation, leading to possible thromboembolic events. Performing a 2-step procedure with a long exchange wire in place may produce difficulty with wire control. This can cause perforations and subarachnoid hemorrhage or wire injury of small penetrating arteries leading to parenchymal bleeds or perforator infarcts. It is impossible to precisely assess how many complications were directly related to these design considerations. There were 10 hemorrhages in the periprocedural period. Four were subarachnoid and directly attributed to guidewire perforation. Five were due to parenchymal bleeding “evident within 24 hours of PTAS.” Although these were described as probably related to reperfusion, they could also be due to vessel injury with later evidence of bleeding in a patient on dual antiplatelet medication. Similarly, the added risk from device design for ischemic injury in the more immediate periprocedural period would also be difficult to precisely assess.

Aggressive medical management available to both arms of the SAMMPRIS trial consisted of 2 antiplatelet agents, a statin, and 1 medication from each major class of antihypertensive agents. Patient compliance and risk factor management were managed at each site by a team including a study coordinator, a lifestyle coordinator, and a lifestyle coach. Compliance with medical regiments was closely monitored by the study coordinator including counting patients’ antiplatelet medications. The lifestyle coach met with the patients to develop personal action plans and contacted the patients every 2 weeks for the first 3 months and then monthly thereafter. Additional help was provided for difficult-to-manage patients from a central director. These measures appear to have a significant effect on blood pressure control, lipid-lowering, smoking cessation, and the number of patients that engaged in moderate or vigorous exercise over the initial 4-month period after randomization. Data regarding the long-term affects of these measures are not yet available. Clearly, questions exist as to whether this degree of oversight could be applied long-term to “real-world” situations. In patients who have cardiovascular symptoms, compliance and lifestyle modification may not always prove successful. The use of antithrombotic medications can yield significant compliance issues in patients with prior myocardial infarction or ischemic strokes.

Concerns about the aggressive medical management regimen aside, 1 fact remains: there was a 12.2% 1-year rate of death and stroke up to 30 days and ipsilateral stroke beyond 30 days in the aggressive medical management group. This may be an improvement over the 1-year rate of ipsilateral stroke seen in the WASID study, but is a 12.2% 1-year stroke risk acceptable for this disease? Any endovascular procedure that aims to improve this outcome must have a very low periprocedural complication rate and lower the stroke rate over time when compared with medical therapy.

Can these procedures be performed with a low rate of periprocedural complication? Some factors that could influence the rate of periprocedural complication may not have been optimized in SAMMPRIS. Two prominent factors are lesion morphology and choice of device. The trial mandated that lesions had to be ≤14 mm long and arteries had to have a normal diameter of 2.0 to 4.5 mm. Early in the experience with balloon angioplasty, Mori et al described the Mori classification for anticipated difficulty with angioplasty of intracranial atherosclerotic lesions. Mori A lesions are short concentric lesions <5 mm long, whereas Mori B are 5 to 10 mm long and may be eccentric, and Mori C are >10 mm and may have excessive tortuosity. Mori found higher rates of death, ipsilateral stroke, or ipsilateral bypass being needed after angioplasty moving from Type A (8%) to Type B (26%) to Type C (87%) lesions. Two studies evaluating 92 and 100 patients, respectively, have not found an outcome difference between lesions >7 mm or <7 mm. However, a number of other studies have found lesion length or morphology an important variable in determining procedural success. The Intrastent multicenter registry of 388 cases undergoing stenting found much lower rates of neurological events and death in patients with lesions <5-mm (6.0%) versus 5- to 10-mm lesions (13.6%) or >10 mm lesions (13.6%). Zhu et al found a 12% rate of in-stent restenosis in Mori A lesions, a 40.6% rate in Mori B, and a 50% rate in Mori C lesions. Miao et al reported on 113 patients and a trend toward high rates of restenosis with Mori Type B and C lesions, but the authors felt the analysis may have been hindered by a paucity of Type C lesions in the analysis. Al-Ali et al reported treatment of 159 lesions and found lesions >10 mm were associated with significantly higher rates of restenosis. Another recent multicenter report of 670 treated lesions found Mori A lesions were safer to treat (OR, 0.51; 95% CI, 0.13–0.72; P<0.007) and were less likely to develop restenosis (OR, 0.33; 95% CI, 0.21–0.55; P=0.0001). We do not know how lesion morphology affected the short-term outcome in the SAMMPRIS cases and what that effect will be on the long-term stroke risk.

The endovascular therapists in the SAMMPRIS trial were limited to a single technique and device system. To date, no single device or technique has emerged that conclusively provides low complication rates, reduces stroke risk long-term, and is clearly superior to other available devices. Approaches besides the Wingspan may have intrinsic advantages. Angioplasty balloons are less rigid than self-expanding stents or balloon-expandable stents and are more easily tractable and less traumatic. In addition, the angioplasty balloon and the balloon-expandable stent have some common inherent procedural advantages over the Wingspan system. They can be introduced through a smaller 5-Fr catheter system. They have rapid exchange systems and do not require longer, more difficult to control guidewires. Finally, they are used in single-step procedures. Some authors have been proponents of angioplasty balloons alone without stent placement or using stent rescue where angioplasty has caused a suboptimal result. Angioplasty publications have described relatively low rates of periprocedural complications. Other authors have been proponents of balloon-expandable stents. Some experience has suggested there are high rates of complication with balloon-expandable stents. However, recent publications have suggested that the complication rates with balloon-expandable stents are similar to those seen with self-expanding stents such as Wingspan. Favorable rates of ipsilateral stroke beyond the 30-day period
have also been reported for both angioplasty alone and for balloon-expandable stents.\textsuperscript{23,26,27} However, these are all retrospective reports and the patients have not had the closer scrutiny of a randomized trial. There is currently a corporate-sponsored trial randomizing patients to a balloon-expandable stent versus medical therapy (Vitesse Intracranial Stent Study for Ischemic Therapy), which may provide data from a randomized trial.\textsuperscript{33}

The Wingspan stent system has demonstrated relatively high rates of in-stent stenosis, particularly in the anterior circulation.\textsuperscript{9–11} It is premature to predict how this will contribute to the ongoing stroke risk in the SAMMPRIS patients. Long-term rates of restenosis have not been well established for balloon angioplasty but may be similar to the Wingspan stent. Wojak et al reported a 27.4% rate of restenosis for 71 lesions, which were predominately treated with angioplasty alone.\textsuperscript{27} Siddiqi et al reported a 38.7% rate of restenosis in 66 patients with balloon angioplasty.\textsuperscript{34} In the same publication, balloon-expandable stents showed a 34% rate of restenosis in 68 patients, suggesting that balloon-expandable stenting did not improve restenosis rates.\textsuperscript{34} A small number of publications with limited patient numbers and limited follow-up have suggested that drug-eluting stents may reduce restenosis rates.\textsuperscript{35–38} A recent report showed a 5-fold decrease in restenosis rates in patients treated with a drug-eluting angioplasty balloon as compared with conventional angioplasty balloons (9% versus 50%).\textsuperscript{39}

The results of the SAMMPRIS trial should not stop further investigation of endovascular therapy for severe symptomatic intracranial stenosis. The trial gave us useful information regarding the outcome for these symptomatic patients with medical management showing that even with aggressive highly monitored medical management, there was a 12.2% combined 30-day stroke and death rate or ipsilateral stroke rate beyond 30 days in the first year of treatment. The first-generation device used in the trial has potential design flaws and demonstrated high rates of periprocedural complication, seemingly unrelated to experience. A high combined rate of periprocedural complication and ipsilateral strokes has been seen with this device in 2 prospective registries and 1 randomized trial. In addition, the trial may not have selected an ideal group of patients for endovascular treatment based on lesion morphology. The SAMMPRIS trial was successful in 1 important way: it set a higher bar for the investigation of endovascular therapy for symptomatic intracranial stenosis.

Ultimately any endovascular therapeutic approach will need to be evaluated in a randomized trial. Selection of any endovascular approach should require prospective single-arm evaluations of the device.\textsuperscript{40} There will need to be close, impartial scrutiny of treatment results. Patients participating in these studies should have inclusion and exclusion criteria that would closely match anticipated randomized trials. The future for endovascular therapy in the management of this disease lies in its ability to demonstrate a benefit for those patients still at high risk for stroke, even with aggressive medical therapy.

Disclosures
Dr Marks has been a consultant for Codman and Shurtleff, Inc (<$10 000).

References


