Emerging Therapy Critiques

Section Editors: Sean I. Savitz, MD, and Heinrich P. Mattle, MD

Critique of “Stenting Versus Aggressive Medical Therapy for Intracranial Arterial Stenosis” by Chimowitz et al in the New England Journal of Medicine

Alex Abou-Chebl, MD; Helmuth Steinmetz, MD

Abstract—Symptomatic intracranial stenoses are an important cause of stroke and have a high risk of recurrent stroke with medical therapy. The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Arterial Stenosis (SAMMPRIS) trial unexpectedly showed a higher-than-expected rate of complications with intracranial stenting and a lower-than-expected recurrence rate with medical therapy. In this commentary, the authors review possible explanations for these findings and suggest future strategies for study. (Stroke. 2012;43:616-620.)

Key Words: angioplasty ■ intracranial stenosis ■ stent

See related article, 580.

Results of the randomized controlled trial of Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Arterial Stenosis (SAMMPRIS) were recently published.1 The SAMMPRIS study enrolled 451 patients with a recently (<30 days) symptomatic (transient ischemic attack or minor stroke) 70% to 99% intracranial atherosclerotic stenosis (ICAD). The patients received either aggressive medical therapy (AMT) or AMT plus percutaneous transluminal angioplasty and stenting (PTAS). AMT consisted of 325 mg aspirin per day plus 75 mg clopidogrel per day for 90 days, rosuvastatin (target low-density lipoprotein <70 mg/dL), antihypertensives (systolic blood pressure <140 mm Hg, <130 mm Hg for diabetics), and lifestyle modification; PTAS was performed using the Wingspan stent system (Stryker Inc). Enrollment was stopped in April 2011 because the 30-day rates of stroke and death were 14.7% (10.2% ischemic, 4.5% hemorrhagic) with PTAS versus 5.8% with AMT (P=0.002). The 30-day risk of PTAS was approximately twice as high as previously assumed2–4 and the 30-day risk under AMT alone was approximately half of that predicted from the Warfarin and Aspirin for Symptomatic Intracranial Stenosis study (WASID).5,6 Patients surviving the first 30 days without an end point had the same likelihood of subsequent stroke in the affected territory.1 What are the implications and possible criticisms of these remarkable findings?

SAMMPRIS, North American Symptomatic Carotid Endarterectomy Trial, European Carotid Surgery Trial, and WASID

There are parallels between SAMMPRIS and previous surgical landmark studies. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) were the first studies to prove the efficacy of a nonmedical neurovascular intervention, that is, carotid endarterectomy in patients with symptomatic >50% extracranial stenoses.7–9 An important observation of these trials was that stroke risk in the affected territory declined steeply with time after study inclusion, even in the medical arm, and 2 years after randomization into the NASCET, patients’ risk in the surgical or medical arms became equal.10 In addition to the negative extracranial–intracranial bypass trial,11 these findings further shifted the scientific focus from “hemodynamics” toward “plaque vulnerability” and artery-to-artery thromboembolism as the more important factor of atherothrombotic stroke.

The WASID study was the first randomized controlled trial for symptomatic intracranial stenosis. In WASID, the risk of recurrent stroke was elevated in those enrolled ≤17 days from the qualifying event and it is known that the highest risk of stroke is within the first few days after an event.5,12 In SAMMPRIS, there was an average of 7 days (range, 4–19 days) between the qualifying event and randomization; half of PTAS patients with later intracerebral hemorrhage (ICH) were treated beyond 17 days.1 Patients had to undergo
cerebral angiography with a centralized review before enrollment.\textsuperscript{13} This made the selection process more rigorous but may have prolonged the time to randomization; an additional effect of this is the increase in the number of procedures that likely contributed to the excessive angiographic stroke risk (1.3\%) noted in the PTAS arm, which was markedly higher than the expected rate of close to 0\%.\textsuperscript{14} The delayed enrollment may have created a selection bias with artificially lower event rates in the medical arm because patients who had severe hemodynamic stenoses may have had recurrent events or orthostatic symptoms leading to exclusion or stenting outside the trial. These medical therapy failure patients may have benefited the most from PTAS.

Early revascularization is superior to delayed treatment in patients with symptomatic cervical internal carotid artery stenosis because of the risk of early recurrent stroke.\textsuperscript{15} This has also been noted with coronary artery disease (CAD); the comparison of ICAD to CAD is particularly relevant because the intracranial and coronary arteries are similar in size and are treated with the same drugs (eg, statins, antiplatelets, etc) and devices (coronary balloons and stents; in fact, the Gateway balloon used in SAMMPRIS is a slightly modified Maverick coronary balloon [Boston Scientific Inc]). In a randomized trial of 2287 patients with stable angina treated with AMT or AMT plus percutaneous coronary intervention, AMT was the superior approach.\textsuperscript{16} However, patients with stable angina and perfusion imaging documenting inducible ischemia had better outcomes with early percutaneous coronary intervention.\textsuperscript{17} Similarly, patients with unstable angina or acute ST-segment elevation myocardial infarction have fared much better (reduced mortality and infarction) with early percutaneous coronary intervention than with AMT.\textsuperscript{18}

There is concern that ultra early intervention in patients with stroke can be associated with a higher risk of complications; however, in SAMMPRIS, the risk of complications (hemorrhagic and ischemic) did not seem to be related to the timing of the PTAS from the qualifying event. In the largest data set of PTAS for ICAD, which included 630 patients, PTAS within 24 hours of the index event, but not beyond, was associated with increased risk of complications.\textsuperscript{19} Given this, it may be best moving forward to enroll patients as soon as possible after the first 24 hours of the qualifying event.

**Plaque Biology and Individual Risk Modeling**

Pathological studies and advanced imaging have confirmed another similarity with CAD, namely that “unstable” carotid plaques are characterized by surface rupture, luminal thrombi, inflammatory activity, and neovascular and intraplaque hemorrhage.\textsuperscript{20,21} Even in a highly effective procedure such as carotid endarterectomy for symptomatic stenoses, individual risk modeling suggests that the overall surgical benefit is generated in a relatively small, <20\%, proportion of operated patients.\textsuperscript{22} This “medical high-risk subgroup” (with a large surgical benefit) was characterized by the combination of irregular carotid plaque surface, higher degrees of stenosis, and more recent ischemic events. Similarly, microemboli derived from extracranial and intracranial unstable plaques can be detected using transcranial Doppler ultrasound.\textsuperscript{23,24} These direct and indirect measurements of “plaque vulnerability” are strong predictors of stroke.\textsuperscript{25} Lesion scoring systems have been developed that reliably predict adverse events with percutaneous transluminal coronary angioplasty\textsuperscript{26} as well as PTAS for ICAD (ie, Mori classification).\textsuperscript{27}

In SAMMPRIS, patients were enrolled based on lesion severity only without functional imaging and there was no distinction between the different subtypes of ischemia. WASID showed that patients with poor collateral flow were at the highest risk of stroke.\textsuperscript{28} Patients with perforator syndromes were also included in SAMMPRIS. This may explain the high risk of perioperative stroke. Of the 33 periprocedural strokes, 23 (69.7\%) were ischemic and of these, 12 of 23 (52\%) were perforator strokes (Fiorella D. SAMMPRIS Interim Results. SVIN 4th Annual Meeting; Westin Diplomat, Hollywood, FL; October 23, 2011). Patients presenting with perforator ischemia may have an excessive risk of perioperative stroke, typically a complete infarction in the territory of the perforator that caused the qualifying event.\textsuperscript{29,30} PTAS restores luminal diameter by pushing the plaque against the vessel wall, which can result in plaque shifting, further occluding stenosed perforators. Exclusion of these patients from SAMMPRIS could have prevented half of the ischemic strokes reducing complications to 9.4\% (21 of 224). Patients presenting with distal, cortical ischemia may not have perioperative perforator occlusion due to the presence of adequate collateral flow. Eccentric plaque location on the ventral aspect of the middle cerebral artery and basilar artery, were there are no perforators, may also decrease the risk of perforator occlusion; animal experiments have shown stent struts do not occlude perforators in healthy vessels.\textsuperscript{31} Regardless of the pathogenesis, the purpose of PTAS is to restore flow to the distal territory supplied by the parent vessel; therefore, PTAS is unlikely to be of benefit in patients with perforator syndromes and exposes them only to risk.\textsuperscript{30}

Vessel size is another variable affecting outcomes and in SAMMPRIS, vessels between 2 and 4.5 mm in diameter were treated. The treatment of very small vessels, that is, <2.5 to 2.75 mm diameter, is problematic. Smaller vessels are more likely to have restenosis and acute thrombosis but they may also be more prone to injury with PTAS. The reasons for the latter are that smaller vessels are more difficult to measure accurately increasing the risk of oversizing of balloons and stents greatly increasing the risk of vessel injury and ICH.\textsuperscript{32,33} In a randomized trial of percutaneous coronary intervention for CAD, vessels <2.75 mm had a major adverse event rate of 12.1\% versus a 7.1\% rate in larger vessels (hazard ratio, 1.720; \(P=0.0412\)).\textsuperscript{14} In SAMMPRIS, there were 4 cases of vessel perforation and 6 other cases of ICH. Although in the publication of the SAMMPRIS trial the authors write that vessel size was not related to the risk of complications, there was a greater risk of ICH (10\% versus 0\%) if the presten lesion diameter was <0.6 mm versus >0.6 mm (\(P=0.0006\)); the mean lesion diameter was 0.3 mm in those with ICH versus 0.6 mm without ICH (\(P<0.0001\)). It is unclear why vessel size did not emerge as a risk factor in SAMMPRIS but the publication did not state if the analysis was performed in a continuous or dichotomous method, which could have a significant impact on the probability of finding a correlation.
given the small number of events. Another possibility that has not been considered previously is that the WASID method for assessing vessel size uses the proximal vessel as a reference but if there is diffuse disease of that vessel, then the reference diameter for stenosis measurement is the distal parent vessel, for example, if there is diffuse middle cerebral artery disease, then the terminal internal carotid artery diameter is used as a reference, which is often ≥1 mm larger than the middle cerebral artery.5 This would not only confound the association between vessel size and the risk of complications, but it could also result in oversizing of devices increasing the risk of ICH. For patients with vessels <2.5 mm, alternative strategies such as angioplasty alone or even staged procedures may be safer alternatives33 and for those with vessels <2 mm in diameter, endovascular therapy may not be a safe option.

Thinking about consequences of SAMMPRIS, in selecting patients for future studies of PTAS for ICAD, it may be worthwhile to use lesion-based risk models that include: lesion severity, eccentricity, calcification and length, vessel size, presence of large branches within the stenotic segment, the absence of adequate angiographic collaterals, the presence of hemodynamic compromise as evidenced by functional imaging or orthostatic ischemia in the distal vascular bed, and differentiation of hemodynamic, embolic, and perforator lesion patterns.

### Improved Medical Treatment

The 30-day and 1-year event rates in the AMT group were 5.8% and 12.2%, respectively, approximately half of the rates noted in WASID.5,6 AMT in SAMMPRIS went far beyond what was mandated in WASID or the carotid endarterectomy trials. It included regular phone calls by a case manager; regular checks and targets for physical exercise, weight, blood pressure, low-density lipoprotein, and HbA1c levels; and free-of-charge treatment with rosuvastatin and antihypertensives.

The lower-than-expected event rate may have also been due to the combined use of aspirin and clopidogrel. This combination has been proven highly effective in preventing recurrent cardiovascular events in patients with CAD and it is not surprising that the benefit in the similarly sized cerebral vessels was significant.35 SAMMPRIS has finally defined what the maximal medical therapy regimen for symptomatic ICAD should be and it includes dual antiplatelet agents for 90 days.

### Procedural Considerations

Lessons learned from the carotid revascularization trials were: the importance of patient and surgeon selection and correctly performed procedures. The majority (25 of 33 [75%]) of the events in SAMMPRIS occurred within 24 hours of PTAS implicating a procedural factor. There were 4 immediate periprocedural subarachnoid hemorrhages due to “wire perforation.”29 The parenchymal ICHs were also temporally closely related to the PTAS; 5 occurred within 24 hours. The investigators felt that these were related to the cerebral hyperperfusion syndrome. Per protocol, systolic blood pressure was kept <150 mm Hg postoperatively. After both carotid endarterectomy and carotid angioplasty and stenting, maintaining low systolic blood pressure decreases the risk of hyperperfusion syndrome. In a study of 836 patients undergoing carotid angioplasty and stenting, which may be most relevant here given that carotid angioplasty and stenting and PTAS are closely related, aggressive systolic blood pressure-lowering to <120 mm Hg greatly reduced the risk of ICH.36 It is possible therefore that some of the ICHs may have been avoidable with a more stringent blood pressure protocol. However, it is difficult to be certain that all of the ICH in SAMMPRIS were truly due to hyperperfusion syndrome because the peak incidence is 3 to 5 days postrevascularization;36 therefore, some intraprocedural event may have been responsible for the ICH, especially because almost all patients were treated under general anesthesia (GA). This confounds the ability to determine when ICH actually occurred because symptoms may not have become manifest until patients were awakened.

This is not the only drawback of GA. There have been some previous studies that have shown that GA is not necessary for a variety of neuroendovascular procedures including PTAS.29,37 The major potential advantage of awake interventions is the ability to examine patients during the procedure to be able to detect neurological deficits earlier and react more quickly to prevent more injury. Awake patients are able to express pain that is critical in detecting such circumstances as severe vasospasm, wire migration, intimal injury, or excessive balloon dilation.39 An attentive interventionist, on detecting pain, can immediately search for the cause, potentially averting injury. Although there has never been prospective validation of the superiority of minimal sedation over GA, the opposite is also true: there has never been a randomized study that showed that GA is needed or safe. Proponents of GA feel that minimizing patient movement is essential to prevent wire perforation. There are no data to support this and in the worst case scenario of awake stroke interventions, there was no increase in risk of ICH in 552 of 980 patients treated awake, but there was an approximately 2-fold risk of death or poor neurological outcome with GA.38 In SAMMPRIS, the known wire perforation rate was 1.7%, which is markedly higher than with coronary percutaneous transluminal coronary angioplasty, despite continuous cardiac movement.39

The SAMMPRIS protocol called for crossing the lesion with a microcatheter first and then exchanging for the balloon, but this could lead to accidental wire movement, a major cause of perforation.13 In the modern era with very deliverable balloon catheters, there is no need for this potentially risky step. The cardiac literature,40 but also some series of PTAS for ICAD, has shown that crossing the lesion with the wire followed by the balloon is sufficient.29,32

The SAMMPRIS authors reported that there was no correlation between balloon size or the ratio of the balloon to the stent and the risk of ICH.1 However, these are not the important factors; the ratio of the balloon to the normal vessel size is. It is the angioplasty that induces the controlled “tear” in the vessel and oversizing the balloon increases the risk of vessel injury.32,33 The Wingspan stent is self-expanding and is typically sized 0.5 mm (or more) larger than the vessel and by
itself does not exert sufficient force to tear the vessel. By calculating the ratio of balloon to stent, any association with oversizing of the balloon would thus be negated. The authors should present the data on ratio of balloon size to the normal (not parent vessel as discussed previously) vessel diameter.

There were only 2 (0.89%) cases of stent thrombosis, which is low but potentially preventable by not stenting vessels smaller than 2.5 mm, ensuring adequate final luminal diameter and adequate platelet inhibition;41,42 although controversial inadequacy platelet inhibition is a real phenomenon and should be considered in any case of stent thrombosis or ischemic complication.43 In SAMMPRIS, postdilation of the stent was permitted, but it is unclear how often it was performed because only 19.5% of patients required a “second balloon” (Fiorella D. SAMMPRIS Interim Results. SVIN 4th Annual Meeting; Westin Diplomat, Hollywood, FL; October 23, 2011); it will be important that future analyses of SAMMPRIS determine the association among final lumen diameter, postdilation, and complications as well as long-term outcomes.

One possible explanation for the higher-than-expected event rate is operator experience. There was no such association in SAMMPRIS, which is unexpected because with most surgical procedures experience is associated with improved outcomes (eg, carotid angioplasty and stenting)14,45 and in SAMMPRIS, there was a marked difference in complication rate based on the volume of enrollment with an 8% ICH rate at sites enrolling <12 patients versus 2% at sites enrolling ≥12 patients (P<0.051; Fiorella D. SAMMPRIS Interim Results. SVIN 4th Annual Meeting; Westin Diplomat, Hollywood, FL; October 23, 2011). SAMMPRIS did have a vetting process for interventionists who had to submit 20 cases for review but only 3 cases had to be with the Wingspan system; angioplasty alone was also sufficient and it did not have to be experience treating atherosclerotic disease.13 There are important differences between the Wingspan stent and the stents used for aneurysm remodeling. In addition, there are major differences in behavior of atherosclerotic lesions to PTAS compared with vasospastic lesions. The inadequacy of operator experience in SAMMPRIS is further suggested by the higher-than-expected rate of angiographic stroke14 and the number of patients (9%) in SAMMPRIS who received 2 stents (Fiorella D. SAMMPRIS Interim Results. SVIN 4th Annual Meeting; Westin Diplomat, Hollywood, FL; October 23, 2011), a marker for improper placement, underestimation of lesion length, or significant dissection and something that is associated with increased complications. The important question is what was the risk of complications based on previous operator experience using the Wingspan system in the treatment of atherosclerotic disease? Then and only then might the real association between experience and complications be found.

Final Comments
The SAMMPRIS trial represents the first effort to validate the safety and efficacy of PTAS for the treatment of symptomatic ICAD. The remarkable medical arm results have now defined what constitutes maximal medical therapy bringing ICAD treatment fully in line with what has been proven effective in the treatment of CAD. On the other hand, the disappointing PTAS results have reminded us of the importance of patient and proceduralist selection as well as the necessity of incorporating all relevant medical knowledge into our practice and study designs even if the knowledge is culled from other specialties, that is, “there is no need to reinvent the wheel.” PTAS is a very risky procedure but should not be written off as unsafe based on just the SAMMPRIS results, which among other things may not replicate outcomes using other stent systems, for example, balloon-expandable stents.19,30 Like carotid revascularization and percutaneous transluminal coronary angioplasty, lessons learned from early failures will lead us to develop better trials and therapies. PTAS remains a valuable tool for patients refractory to medical therapy and should continue to be considered as investigational to be performed in highly selected patients by those experienced in the treatment of ICAD.

Disclosures
Dr Abou-Chebl is a local Principal Investigator for the Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT) trial (stenting for ICAD) and is on the speaker’s bureau at BMS/Sanofi.

References


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