Intracranial Stenting With Wingspan
Still Waiting a Safe Landing
Alex Abou-Chebl, MD


Intracranial atherosclerotic disease (ICAD) is a major cause of stroke and yet there are no proven effective treatments for it. Medical therapy has been associated with a high rate of recurrence, particularly in those with the most severe stenoses who have a 22.5% risk of stroke or death in the first year after a stroke. Clearer better alternatives are needed. Surgical bypass has been shown in at least 1 trial to be worse than medical therapy in the era before thienopyridines, statins, and angiotensin-converting enzyme inhibitors. In this issue of Stroke, Fiorella and colleagues describe their longer-term experience with intracranial stenting with the Wingspan (Stryker Inc, Fremont, CA) stent system and last year in this Journal, Jiang and colleagues published their long-term experience with 100 consecutive patients also treated with the Wingspan stent system. The question is do these publications broaden our knowledge enough to alter management of patients with ICAD? Do they prove that endovascular therapy is superior to medical treatment and that it is safe enough to be performed routinely?

The article by Fiorella et al represents the largest (N=158) published series of Wingspan in the United States to treat ≥50% symptomatic stenoses. The immediate perioperative stroke and death rates were 5.7% (N=9) and 2.5% (N=4), respectively. Over a mean follow-up period of 14.2 months (only 110 patients [69.6%] had 12 months of follow-up), the primary end point (any perioperative stroke or death and any ipsilateral stroke thereafter) was noted in 15.7% of patients or approximately 13.2%/year. Seventy-six percent of the ipsilateral stroke (75% subgroup in Warfarin-Aspirin Symptomatic Intracranial Disease [WASID] and far greater than the approximately 12%/year rate seen overall). The results by Jiang et al are more favorable toward stenting, particularly because they treated the highest-risk (>70% stenosis) patients.

There were many notable differences between the 2 studies. To begin with, the outcomes in the Fiorella et al study were not determined by independent neurologists but by “investigators at the individual sites,” whereas Jiang et al used independent stroke neurologists. On the other hand, some (percentage unknown) of the follow-up in the latter study was by “telephone.” Jiang et al published detailed exclusion criteria including: age ≥75 years, lesions >15 mm long, <2 mm diameter, and cardiac sources of embolism. The study by Fiorella et al does not detail any patient or lesion characteristics as either inclusion or exclusion criteria. There were also major differences in the interventional protocols; although both groups gave their patients aspirin and clopidogel, Jiang et al gave every patient intravenous nimodipine intraoperatively and postoperative Fraxiparine. Fiorella et al reported a 30-day mortality rate of 2.5%, which raises concern. This may be explained by the younger age (mean age was 53 years versus 63 years) of the patients treated by Jiang et al and/or by procedural factors such as differences in operator experience (Jiang et al: 105 lesions treated by 2
interventionists versus Fiorella et al: 168 lesions treated by 13 interventionists). Additionally, Jiang et al performed almost all (98%) of their procedures in awake patients; Fiorella et al do not discuss the anesthetic method used but, based on prior publications, most were likely treated under general anesthesia. There are drawbacks to stenting in anesthetized patients (general anesthesia been associated with increased mortality and decreased neurological outcomes after intra-arterial therapy for acute ischemic stroke) and the feasibility and safety of awake interventions has previously been presented.4,5

So it would seem these 2 studies do broaden the knowledge base but at the time of this editorial, the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial had just been halted. This was a randomized trial of best medical therapy versus angioplasty and stenting with the Wingspan system plus best medical therapy in patients with symptomatologic 70% ICAD. There is much that remains unknown at this time; however, what is known is that after enrolling 451 patients, the data safety monitoring board recommended that the trial be halted due to a 14% 30-day rate of stroke or death with stenting compared with 5.8% in the medical arm, which was a “highly significant difference” (National Institute of Neurological Disorders and Stroke Clinical Alert, April 11, 2011). The anticipated 30-day event rate in the interventional arm was 5.2% to 9.6%, based in part on some of the data presented by Fiorella et al, and 10.7% in the medical arm. This 14% event rate is approximately 2.8 times that noted in the 2 studies by Fiorella et al and Jiang et al; therefore, we will have to reconcile the results from these 2 studies with those seen in SAMMPRIS when the full results are published.

Although the official SAMMPRIS results have not been fully released, these 2 studies have to be viewed in the context of a post-SAMMPRIS world, in which the utility of their results is unfortunately diminished. However, if we take this as an opportunity rather than a setback, we can rethink our approach to ICAD, both medical and endovascular, because both are currently inadequate. To understand how to improve treatments, we have to understand the shortcomings of our data sets. What is missing from the currently available data are unified definitions of symptomatic status and TIA, appropriate patient selection criteria including differentiation between patients who have hemodynamically significant stenoses with distal territory hypoperfusion and those who have primarily artery-to-artery emboli or both. This is important because patients with artery-to-artery emboli may do better with medical therapy that includes dual antiplatelet agents compared with those who are “pressure-dependent” and have orthostatic cerebral ischemia despite medical therapy. The latter may in fact do better with stenting but many of whom may have been excluded from the randomized trials biasing the trials toward medical therapy. Also what has not been discussed in the published literature is whether patients presented with perforator syndromes due to branch origin stenosis. These patients who present with pontine or basal ganglia “lacunar” infarcts or recurrent TIAs in those territories who also have concomitant basilar artery or middle cerebral artery stenosis at the site of origin of the perforator may not be ideal candidates for stenting. The purpose of stenting is to restore nonturbulent flow to the distal territory and stenting will cause plaque shifting into the ostia of the perforators completing the infarct.8 This was not an exclusion criterion in the Fiorella or Jiang studies or SAMMPRIS.

There are many unanswered questions regarding the endovascular techniques, particularly whether it was wise not to postdilate after deploying the Wingspan stents. The instructions for use prohibit postdilation presumably to avoid stent strut fracture, but to not do so may increase the risk of acute and subacute stent thrombosis and early restenosis. In my practice, I postdilate all Wingspan stents to ensure optimal stent wall opposition as well as to maximize the residual lumen area, which is the best predictor of restenosis, a fact learned from my interventional cardiology colleagues. Interventional cardiologists have amassed a wealth of information on angioplasty and stenting of vessels similar in size to the cerebral vessels and affected with the same disease. These data include information on optimal periprocedural and maintenance medical management, who should have stenting, who is at highest risk for perioperative events and restenosis, how to avoid periprocedural events and restenosis, which devices are better than others, how to monitor for restenosis, how to manage restenosis, etc. In short, the answers to many of the questions that remain outstanding in the management of ICAD may already be available in the coronary literature. For example, dual antiplatelet therapy has clearly been proven essential and its prolonged use is associated with better outcomes compared with aspirin monotherapy in patients with coronary stents.6 The cardiac literature is replete with studies of variable clopidogrel and aspirin response, which have been associated with a markedly increased rate of periprocedural adverse events, including acute stent thromboses. An assessment of clopidogrel response was not part of the SAMMPRIS trial and has only been mentioned in a few reports of intracranial interventions. In addition, postoperative heparin has been associated with increased complications and no significant benefits after coronary artery stenting, yet many reports of stenting for ICAD, including the article by Jiang et al, describe prolonged heparin use, some with an associated increased rate of intracerebral hemorrhage.6,7 Almost all coronary stents on the market today are balloon-expandable not self-expanding like Wingspan. Although self-expanding stents were touted to continue to expand after placement and to decrease the risk of restenosis, the reality was that they incited greater neointimal proliferation and the same degree of late luminal loss.8

The most important information we can glean from the cardiac literature is how to select patients for stenting and how to reduce complications and restenosis. For example, diabetic patients and those with small vessels (ie, <3 mm diameter but especially <2.5 mm diameter) have among the highest rates of restenosis. Although Jiang et al did not stent patients with vessels <2 mm, Fiorella et al do not give us this information or the information on who developed restenosis; on a related note, restenosis and TLR are considered major adverse events in the coronary literature and they need to be reported as such in the neurointerventional literature. Ensuring complete stent expansion and wall opposition, especially in calcified lesions, and detection and treatment of residual
dissections can prevent acute thrombosis. The coronary literature also tells us that powerful tools for the reduction of restenosis are the drug-eluting stents. There are many other facts that can help us design better trials and devices for the treatment of ICAD. Briefly, however, what is needed now is: (1) a concerted effort to better define which patients are best treated with medical therapy and which by endovascular therapy; (2) standardized definitions of qualifying events and outcomes; (3) functional imaging in all patients to determine that distal territory tissue is at risk rather than tissue supplied by perforators; (4) definitions of which patients have atherosclerosis as the etiology as opposed to vasculopathies or vasculitides; (5) a standardized, well thought out endovascular approach that takes into account the vast knowledge base gained from the endovascular treatment of coronary artery disease; (6) validation studies of the potential benefits of awake interventions; (7) next-generation devices that minimize the neointimal response yet that are easily and safely delivered to the cerebral vessels; (8) mandatory cerebral angiography in all patients to provide the true denominator for rates of restenosis and stent thrombosis along with angiographic definitions of both that take into account the continuous rather than dichotomous nature of in-stent stenosis; (9) standardized perioperative and postoperative antithrombotic therapy as well as universal risk factor modification; (10) patient and caregiver education must be standardized and given to all with emphasis on compliance with dual antiplatelet and disease-modifying therapies; and (11) long-term follow-up for 5 to 10 years must also be performed because of the risk of atherosclerotic lesion recurrence/progression that differs from the early cause of in-stent stenosis, neointimal hyperplasia.

Finally, we need to move away from an endovascular dogma that says “my mentor or chief did it this way so it must be the right way” to a more rigorous scientific approach that is focused on understanding the disease and one that is not afraid to acknowledge that physicians of other specialties may have answers to our most pressing questions. We do not need to reinvent the endovascular wheel for every vascular bed; our patients with ICAD deserve better.

Disclosures

The author is the site Principal Investigator in the Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT) trial of a balloon-expandable stent sponsored by Micrus Endovascular, Inc and is on the Speakers’ Bureau for the BMS/Sanofi partnership.

References


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