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Where are we heading in post-China angioplasty and stenting for symptomatic intracranial severe stenosis era?

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Abstract:

Symptomatic intracranial atherosclerotic disease (ICAD) is a globally challengeable disease. In the past 20 years, people have made a huge effort to deal with the problem including using endovascular technology and aggressive medical therapy. However, the efficacy of these methods seemed to be limited. The recent China angioplasty and stenting for symptomatic intracranial severe stenosis (CASSISS) did not support the addition of percutaneous transluminal angioplasty and stenting to medical therapy for the treatment of patients with symptomatic severe ICAD. So where are we heading in the post-CASSISS era?

Keywords:

China angioplasty and stenting for symptomatic intracranial severe stenosis, intracranial atherosclerotic disease, stent

Symptomatic intracranial atherosclerotic disease (ICAD) occurs with high morbidities and remains to be a challenge for many clinicians. Aspirin or warfarin to prevent stroke (WASID) trial, the first randomized clinical trial of ICAD, has shown a high ischemic stroke rate in the territory of a symptomatic intracranial stenosis at one year was 11% (warfarin) and 12% (aspirin).[1] It has been found that the risk of a subsequent stroke remains to be high especially with stenosis greater 70%.[2] Moreover, the medical management for ICAD is not readily available for many patients in rural areas and low income countries.

In order to overcome these challenges, endovascular technology, such as stent placement, was developed. Wingspan stent was the first device with reasonable expectations and underwent a large multicenter randomized controlled trial (RCT) study (i.e., Stenting vs. aggressive medical management for preventing recurrent stroke in intracranial stenosis [SAMMPRIS]) in which the stent placement procedure was combine with Gateway balloon. However, stent technology was still premature at the time. In fact, the findings from SAMMPRIS implied that the benefit of Wingspan stent appeared to be overestimated while undermining the efficacy of aggressive medical management.[3] In addition, the results from Vitesse Stent Ischemic Therapy (VISSIT) study subsequently questioned the strength of evidence for intracranial endovascular treatment.[4]

After SAMMPRIS trial was completed, the developer of Wingspan stent (i.e., Stryker) was required to complete a post market surveillance study of the wingspan stent system (WEAVE trial) by FDA.[5]

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Interestingly, WEAVE trial showed significantly lower risk of perioperative complications associated with stent placemen than SAMMPRIS (2.6% vs. 14.7% within 30 days); this was largely due to the strict sample inclusion criteria. In fact, Gao *et al*.[6] published a large multicenter RCT (China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis [CASSISS] trial) in the Journal of the American Medical Association shortly after WEAVE trial. The trial could recruit as many study subjects as SAMMPRIS because of large prevalence of ICAD in Asian populations. The study denoted low perioperative complications associated with stent placement similar to WEAVE trial once sample inclusion criteria were strictly followed. Nevertheless, the study concluded that there was no significantly additional benefit with stenting though the safety of stent was found to be comparable to that of medical therapy alone for ICAD.

Available data appear to show uncertain results about the efficacy of stenting as the sole treatment modality for ICAD. However, it has been more than ten years since SAMMPRIS trial was published and CASSISS trial helped stenting remain to be a viable treatment option with its safety profile comparable to that of medical therapy. It seems stenting still has clinical potentials that have not been fully appreciated and premature to abandon this treatment modality as an alternative option.

What should we do then? There are a few areas that can help improve the efficacy of stenting. First, patient selection for endovascular therapy can be strictly controlled. The typical inclusion criteria include (1) age 22-80 years old, (2) symptomatic intracranial atherosclerosis stenosis of 70%–99%, (3) preoperative mRS Score ≦3, (4) at least two strokes related to the responsible vessel supply area and at least one stroke during standard drug therapy, and (5) and the time of last symptom occurrence more than 8 days from the time of operation. In addition, endovascular therapy is a reasonable option during post-stroke period for patients with ICAD who have failed intensive medication. These criteria were one of the reasons for the reduction of perioperative complications in WEAVE and CASSISS trials.

Second, there may be differences in delivering "high-quality" care for those who undergo endovascular therapy. The differences are typically observed due to different amount of experiences in stenting procedure and perioperative management. Although SAMMPRIS trial assumed experiences of interventional operators did not significantly affect the results of the study, it would be more reasonable to surmise higher rates of successful stenting with more clinical experiences. In fact, one of the strengths from CASSISS trial was based on the prevalence of ICAD in Asian populations, which ultimately produced more opportunities to build experiences for clinicians and practice strict patient selection. Intraoperative monitoring of activated coagulation time (ACT) was another example to indicate discrepancies of quality of care in SAMMPRIS trial. The trial noted an absolute increase of perioperative bleeding associated with stenting. The study explained that ACT was maintained in 250 to 300 seconds (normal range) throughout the procedure in 101 of 206 cases (49.0%). However, a *post hoc* analysis revealed that one reason for perioperative complications was abnormally high ACT values from the half of participants, which was significantly associated with hemorrhagic stroke.[7]

Finally, there are large potentials to improve in technology of interventional therapy tools. A large multicenter retrospective study has confirmed that bare metal stent is safe and effective to treat ICAD refractory to medical therapy.[8] Self-expanding stent system has attempted to achieve an easy wire-guiding and stent-delivering method through tortuous and fragile intracranial blood vessels with minimal radial stimulation to the vessel wall. Although awaiting a multicenter trial to demonstrate the efficacy, Enterprise I/II self-expanding stents have been marketed with its easiness to operate and less perioperative complications, which reduces the learning curve for many clinicians.[9,10] Acclino flex stent is a self-expanding German stent that can be delivered through a low profile balloon microcatheter without wire-exchanging maneuvers. Meyer *et al*.[11] have noted the safety and efficacy of the self-expanding stent plus balloon microcatheter for secondary stroke prevention from ICAD. Development of new endovascular devices with features of easiness-to-operate, rapid-exchangeable balloons, and drug-coated balloons continue to simplify the operation and improve periprocedural safety.[12]

Efforts to improve stent therapy must recognize continuous changes in medical therapy for ICAD. Aggressive medical therapy has been supported by the findings from SAMMPRIS trial that undoubtedly showed significantly lower recurrent ischemic stroke rates than that of WASID trial. The high recurrent stroke rate of WASID trial was resulted from the initial medical therapy for ICAD, which merely included single antiplatelet agent.[13] As more clinical studies are conducted to determine the optimal medical therapy (e. g., duration and combination of antiplatelet therapy and/or anticoagulation), techniques and technology of stent therapy should be in accord with its development. Future studies could produce meaningful results to show the role of transluminal angioplasty/stenting, submaximal balloon angioplasty, direct or indirect arterial bypass, and ischemic conditioning for prevention of stroke in patients with ICAD.[14,15]

Insights from the post-CASSISS era:

1. By strictly following the inclusion criteria, rate of perioperative complications associated with endovascular therapy can be reduced
2. Quality of stent therapy can be improved by optimizing operators' clinical experiences and perioperative management
3. Development of new endovascular devices reflect large potentials in stent therapy
4. Efforts to improve stent therapy must continue as medical therapy for ICAD continues to advance.

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Conflicts of interest

There are no conflicts of interest.

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