
The Challenges of Intracranial Revascularization for Stroke Prevention
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The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial\(^1\) (SAMMPRIS, ClinicalTrials.gov number, NCT00576693), as reported by Chimowitz et al. in this issue of the Journal, showed that aggressive medical management alone was superior to intracranial arterial stenting with the use of the Wingspan stent system in addition to aggressive medical therapy in patients with a recent transient ischemic attack or stroke attributed to 70 to 99% stenosis of the diameter of a major intracranial artery. Three key lessons can be gleaned from the SAMMPRIS trial and previous trials of revascularization for stroke prevention: the challenges of intracranial revascularization are greater than those of revascularization of extracranial carotid stenoses; aggressive and attentive medical therapy is an effective approach to the prevention of stroke in high-risk populations; and the Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS) play critical roles in the advancement of cost-effective medicine.

The SAMMPRIS trial is the third randomized trial of intracranial revascularization that has failed to show a benefit of that strategy over medical therapy for the prevention of stroke. Two trials of intracranial–extracranial bypass surgery for the prevention of stroke in patients with symptomatic internal carotid-artery occlusion — the Extracranial–Intracranial Bypass Trial\(^2\) and the Carotid Occlusion Surgery Study (COSS, NCT00029146)\(^3\) — were negative studies, which has led to very limited use of the bypass procedure. Although the bypass surgery in COSS accomplished the physiological goal of improving perfusion of blood to the brain, it was ineffective, as compared with medical therapy, in preventing recurrent stroke.\(^3\) Similarly, stenting in the SAMMPRIS trial decreased the stenosis of the symptomatic artery but was inferior to medical therapy in preventing recurrent stroke.

The 30-day rate of stroke or death associated with stenting in the SAMMPRIS trial (14.7%) is nearly 2.5 times as high as the 6% rate associated with stenting of symptomatic extracranial carotid-artery stenoses in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST, NCT00004732).\(^4,5\) One surprising finding was that symptomatic intracranial hemorrhage, a relatively rare complication after revascularization of extracranial carotid-artery stenosis,\(^6\) represented almost a third of all perioperative strokes in the SAMMPRIS trial. The intracranial hemorrhages were thought to be due to reperfusion hemorrhage or subarachnoid hemorrhage from wire manipulations during the procedure. This latter complication emphasizes the fact that stenting of the intracranial vasculature is technically more challenging than is stenting of the extracranial carotid artery because of the tortuous course of the internal carotid artery through bony canals, an abrupt right-angle turn for the middle cerebral artery, and arterial diameters that are smaller overall than those in the extracranial circulation. Small, penetrating brain arteries from the trunks of the middle cerebral and basilar arteries are often near or at the site of the placement of the stent and may be compromised. The circle of Willis can provide additional pathways for blood flow to the brain in patients with extracranial arterial occlusion, but when there is occlusion of the middle cerebral artery, prevention of ischemic damage relies on cortical collaterals. These anatomical and physiological differences underlie the increased risk of stroke with intracranial revascularization and highlight the point that it is not just the safety of a given device, but the safety of the procedure itself, that must be con-
considered. It is hoped that future analyses of data from the SAMMPRIS trial will clarify whether the recurrent strokes were due to embolism, stent thrombosis, or low perfusion pressure related to a critical stenosis.

Aggressive medical management of risk factors, and possibly the addition of clopidogrel to aspirin in the short term, was associated with unexpectedly lower rates of recurrent stroke at 1 year in the SAMMPRIS trial than were seen in the earlier Warfarin–Aspirin Symptomatic Intracranial Disease (WASID, NCT00004728) study, which had the same entry criteria (12.2% vs. 25%). In addition, after perioperative strokes are excluded, the rate of subsequent ischemic strokes in the territory of the qualifying artery was essentially the same in the stenting and medical-management groups. These observations raise the question of whether current aggressive management of risk factors may be equivalent or superior to stenting or carotid endarterectomy in patients with asymptomatic extracranial carotid stenosis. In contrast, the robust benefit of revascularization for the treatment of severe symptomatic extracranial carotid stenosis is well established.

Finally, CMS played an important role in expediting the conduct of the SAMMPRIS trial. The FDA approved the Wingspan stent for clinical use under a humanitarian device exemption in 2005 and approved the use of the device for the SAMMPRIS trial under an investigational device exemption. However, CMS did not reimburse for the Wingspan device outside of its use in a randomized trial. Recruitment within the trial proceeded quite well. Similarly, CMS, despite lobbying by physicians and industry, reimbursed for carotid stenting in asymptomatic patients only if the stenting was performed within the context of a trial. This action facilitated recruitment into CREST. In contrast, endovascular devices for the treatment of acute stroke have been cleared by the FDA through the 510(k) pathway and reimbursed by CMS without demonstration of clinical benefit. Not surprisingly, the use of these devices in clinical practice is increasing, while recruitment into trials designed to show the clinical efficacy of the endovascular treatment in patients with acute stroke has lagged.

New technology for preventing and treating stroke should be tested in trials that address clinical effectiveness and incorporate the best current medical management of stroke. The FDA and CMS must be consistent gatekeepers for the distribution and diffusion into clinical practice of technology that affects the quality and cost of clinical care.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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This article (10.1056/NEJMe1108394) was published on September 7, 2011, at NEJM.org.