First Food and Drug Administration-Approved Prospective Trial of Primary Intracranial Stenting for Acute Stroke

SARIS (Stent-Assisted Recanalization in Acute Ischemic Stroke)

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Background and Purpose—Acute revascularization is associated with improved outcomes in ischemic stroke patients. However, it is unclear which method of intraarterial intervention, if any, is ideal. Numerous case series and cardiac literature parallels suggest that acute stenting may yield high revascularization levels with low associated morbidity. We therefore conducted a Food and Drug Administration-approved prospective pilot trial to evaluate the safety of intracranial stenting for acute ischemic stroke.

Methods—Eligibility criteria included presentation ≤8 hours after stroke onset, age 18 years or older, National Institutes of Health Stroke Scale score ≥8, angiographic demonstration of focal intracerebral artery occlusion ≤14 mm, and either contraindication to intravenous tissue plasminogen activator or failure to improve 1 hour after intravenous tissue plasminogen activator administration. Exclusion criteria included known hemorrhagic diathesis or coagulopathy, platelet count <100 000, intracranial hemorrhage, blood glucose level of <51 mg/100 mL, or CT perfusion imaging demonstrating more than one-third at-risk territory with nonsalvageable brain (low cerebral blood volume). Data are presented as mean±SD.

Results—Twenty patients were enrolled (mean age, 63±18 years; 14 women). Mean presenting National Institutes of Health Stroke Scale was 14±3.8 (median 13). Presenting thrombolysis in myocardial infarction score was 0 (85% of patients) or 1 (15%). Recanalization to thrombolysis in myocardial infarction score of 3 (60% of patients) or 2 (40% of patients; P<0.0001) was achieved. One (5%) symptomatic and 2 (10%) asymptomatic intracranial hemorrhages occurred. At 1-month follow-up, a modified Rankin scale score of ≤3 was achieved in 12 of 20 (60%) patients and a modified Rankin scale score of ≤1 was achieved in 9 of 20 (45%) patients.

Conclusion—This Food and Drug Administration-approved prospective study suggests primary intracranial stenting for acute stroke may be a valuable addition to the stroke treatment armamentarium. (Stroke. 2009;40:3552-3556.)

Key Words: acute ischemic occlusion ■ intracranial stent ■ stroke ■ Wingspan system

Acute ischemic stroke intervention has been galvanized by the correlation of clinical outcome with radiographic revascularization.1–6 Data from multiple, well-designed trials demonstrate that recanalization is associated with improved outcome.1–8 A critical corollary to the importance of recanalization is the importance of time-to-recanalization.6–8 These realizations are directing government policy, reimbursement patterns, and overall physician interest toward increased commitment to developing rapid recanalization tools and creating an infrastructure to ensure patients receive such therapies. However, despite an increasing groundswell in acute stroke endovascular intervention research, substantial ambiguity exists regarding whether endovascular intervention benefits acute stroke patients.

Recent case series9–11 have reported excellent outcomes with self-expanding stents (SES) in patients with acute intracranial occlusions in whom other recanalization methods have failed. Despite using stent deployment as a “salvage” technique in patients with recalcitrant occlusions, these data suggest that stent-assisted revascularization results in high recanalization rates with a reasonable safety profile. However, problems inherent to the data quality of retrospective case series and concerns about early rethrombosis and longer-term durability doubtless exist. We therefore sought and received Food and Drug Administration approval for a 20-patient prospective pilot study to evaluate the safety and efficacy of primary stent deployment for revascularization in acute stroke patients.
Materials and Methods

Food and Drug Administration approval was provided for a 2-center (University at Buffalo, Cleveland Clinic) prospective single-arm trial to evaluate intracranial stenting as a first-line intraarterial (IA) acute stroke treatment for 20 prospectively enrolled patients. Each center was allowed 2 roll-in patients to familiarize themselves with the study protocol and stent-for-stroke technique. The device identified for evaluation was the Wingspan Intracranial SES System (Boston Scientific). The study was conducted between February 13, 2008 and October 6, 2008. Institutional review board approval was obtained from each institution and written informed consent was obtained.

Primary outcome measures included safety and angiographic evidence of recanalization. Safety was evaluated by occurrence of hemorrhage, either symptomatic (defined as >4-point National Institutes of Health Stroke Scale score [NIHSS] worsening in the presence of intracranial hemorrhage [symptomatic intracranial hemorrhage]) or asymptomatic, or deterioration in neurological examination. Recanalization was evaluated by thrombolysis in myocardial infarction (TIMI) score of the target vessel. Secondary outcome measures included clinical outcome measured by discharge NIHSS score (defined as NIHSS score at discharge or last-recorded NIHSS score, obtained on a daily basis by an National Institutes of Health-certified treating physician, before death in the event of in-hospital mortality) and 1-month modified Rankin scale (mRS) score (obtained by a trained certified research nurse/nurse practitioner).

Inclusion criteria were NIHSS ≥8, presentation within adequate time to allow device deployment within 8 hours of the patient being last seen normal, age 18 years or older, angiographic demonstration of focal intracerebral artery occlusion (TIMI 0/1) ≥14 mm, and either contraindication to intravenous tissue plasminogen activator (IV-tPA) or no improvement ≥1 hour after IV-tPA administration. Exclusion criteria included known hemorrhagic diathesis or coagulopathy, presence of intracranial hemorrhage on preintervention CT, platelet count of <100 000, blood glucose level of <51 mg/100 mL, parent vessel diameter of <2 mm or >4.5 mm, or CT perfusion demonstrating more than one-third of the “at-risk” territory as nonsalvageable (ie, with low cerebral blood volume).

Preprocedure CT imaging, including baseline axial CT, CT perfusion, and CT angiography, was obtained on a Toshiba Aquilion 64 scanner (Toshiba America Medical Systems). Perfusion maps were generated by both Gaussian-fit and single-value deconvolution methods using Vitrea software (Vital Images), yielding the following perfusion parameters: time-to-peak, cerebral blood flow, and cerebral blood volume. Four axial perfusion maps were generated for each patient, with the distribution of the maps being chosen to provide maximal coverage of the middle cerebral artery, anterior cerebral artery, and posterior cerebral artery territories, and with the most inferior slice providing information from the superior portion of the posterior fossa.

Procedural technique was consistent with standard, nationally practiced endovascular methods. In brief, clopidogrel (600 mg) and aspirin (650 mg orally/600 mg rectally) were administered preprocedurally to all patients. Access was gained with a 6- to 8-French groin sheath, and then a 5-French diagnostic catheter (interventionist’s choice) was used to select the vessel of interest and perform confirmatory diagnostic imaging. After diagnosis confirmation, an exchange wire was used to remove the diagnostic catheter and provide access for a platform catheter (interventionist’s choice). A heparin bolus was administered and titrated to maintain an activated coagulation time between 250 and 300 seconds. A microcatheter of 0.014 and 0.021 inches (interventionist’s choice) was then navigated over a microwire (interventionist’s choice) to a position just beyond the occlusion. A combined microcather–platform catheter run was performed to document the occlusion length. Patients were enrolled preprocedurally and could only be removed from the study if, at this juncture, diagnostic angiography demonstrated the previously listed exclusion criteria of no occlusion, an occlusion of >14 mm, or a parent vessel diameter of <2.0 mm or >4.5 mm. The microcatheter was then exchanged over an exchange-length microwire, and the Wingspan System was brought into position and deployed in typical fashion. Therefore, successful deployment was not required for enrollment; results were analyzed in an intent-to-treat manner. Additional interventions were allowed if the treating physician felt that further intervention would benefit the patient.

Statistical analysis was performed using Student t test for normally distributed continuous data and Wilcoxon match-pairs signed-rank test for ordinal or nonparametric data. Data are presented as mean±SD.

Results

Twenty patients (14 women) were enrolled. All patients were enrolled from a single center (University at Buffalo) because of administrative delays at the second center. Mean age was 63±18 years. Mean time from stroke onset to intervention was 5 hours and 13 minutes ±1 hour and 54 minutes (median, 4 hours and 52 minutes). Two protocol violations occurred, with patients undergoing intervention >8 hours after stroke onset (1 at 8 hours and 34 minutes; 1 at 9 hours and 43 minutes). The earliest time from stroke onset to intervention was 2 hours and 7 minutes in a patient who had an IV-tPA loading dose but then demonstrated uncontrollable hypertension, causing the treating neurologist to halt further IV-tPA administration. She demonstrated no improvement 1 hour after IV-tPA administration and had been stabilized hemodynamically and, therefore, underwent stent-for-stroke intervention. Total time from procedure onset to vessel recanalization was 45±25 minutes (median, 45 minutes; range, 14 minutes to 2 hours and 9 minutes).

Mean presenting NIHSS score was 14±3.8 (median, 13). Eighty-five percent of patients (n=17) presented with TIMI 0 and 15% (n=3) presented with TIMI 1. Occluded vessels included the right middle cerebral artery (n=11), left middle cerebral artery (n=5), basilar artery (n=3), and right carotid “T” (n=1).

Intracranial SES were placed in 19 of 20 enrolled patients. One patient experienced recanalization with positioning of the Wingspan delivery system before stent deployment. This patient had previously received a partial dose of IV-tPA (National Institute of Neurological Disorders and Stroke loading infusion only) and had shown no clinical improvement, and persistent occlusion was documented on diagnostic angiography. However, with stent delivery system positioning, the occlusion appeared to lyse, with only 1 distal branch (<1.5 mm) remaining occluded. The delivery system was withdrawn and the vessel was observed over time to confirm durability of recanalization. When patency of the target vessel had been maintained for ≈30 minutes, it was felt that stent deployment would be of marginal benefit. Reteplase (4 mg) was intrarotationally administered for the distal occlusion, and the procedure was concluded.

Two patients had excessively tortuous cerebrovasculature that would not allow tracking of the Wingspan System to the occlusion, despite an attempt to do so in each case. In the first patient, an attempt was made with a Merci retriever (Concentric Medical), which did not successfully achieve recanalization; therefore, in keeping with the goal of evaluating SES technology for acute stroke, an alternate, more navigable SES, the Enterprise Vascular Reconstruction Device (Cordis), was then used. In the second patient, the Enterprise was the first alternative therapy after failure of navigation with the
Wingspan. After Enterprise deployment, both patients experienced immediate recanalization. The Table lists the numbers of various brands and dimensions of SES used.

Additional poststent deployment IA therapies were used in 12 patients (60%). These included IA eptifibatide administration (n=10; mean dose, 13.0±1.6 mg), angioplasty (n=8), and IA reteplase (n=2; mean dose, 6±2.8 mg). Two patients had received a full course of IV-tPA before intervention and 1 patient had received a partial course of IV-tPA, all without improvement.

Recanalization was achieved in all 20 patients: 12 (60%) had TIMI 3 and 8 (40%) had TIMI 2 (P<0.0001 vs pretreatment TIMI scores). Thirteen (65%) patients improved after intervention by ≥4 NIHSS points during hospitalization. No patients met the a priori definition of symptomatic intracranial hemorrhage; however, 1 (5%) demonstrated no improvement in NIHSS (NIHSS=20) and had intracranial hemorrhage with mass effect on postprocedure CT; therefore, that result is considered symptomatic intracranial hemorrhage for analysis purposes. Two additional patients (10%) had asymptomatic intracranial hemorrhage. Discharge NIHSS score was 7.4±7 (median, 5; range, 0–20; P<0.0001 vs presentation NIHSS).

At 1-month follow-up, mRS of ≤3 was achieved in 12 (60%) patients and mRS of ≥1 was achieved in 9 (45%) patients. No transient ischemic attacks or neurological worsening to suggest a new cerebral ischemic event occurred between the immediate postprocedure time point and the 1-month follow-up. No symptoms suggestive of stent thrombosis or occlusion were encountered.

The 1-month mortality rate was 25% (5 patients). An 81-year-old woman and an 82-year-old woman (presenting NIHSS scores of 13 and 20, respectively) experienced no change in postprocedure neurological examination; therefore, the families, in accordance with the patients’ previously expressed wishes, elected to withdraw care. A 61-year-old man experienced moderate improvement (preprocedure, NIHSS 18; postprocedure, NIHSS 15); however, when no further improvement occurred in the ensuing weeks, the family transferred him to hospice care, where he died. The remaining deaths occurred in 2 24-year-old men: 1 experienced modest improvement and 1 had dramatic improvement but then experienced mitigating complications. The first young man demonstrated mild improvement with NIHSS of 20 to 17 immediately after the procedure; however, on arrival to the intensive care unit, it became evident that he had severe cardiac output failure. Echocardiography demonstrated 6-cm cardiac vegetation. The patient experienced multiorgan failure attributable to the combined effect of poor cardiac output and multiple visceral embolic events. He died 18 days after intervention. The second young man had a congenital cardiac abnormality requiring anticoagulation therapy. He had experienced 2 previous strokes when not receiving anticoagulation. In order to undergo nasopharyngeal surgery, the patient had ceased taking his anticoagulation. On the day of presentation, upon extubation from that surgery, he demonstrated stroke symptoms (NIHSS=11). A stent-for-stroke intervention was performed with immediate improvement (NIHSS=3). However, ~3 hours after the procedure, he experienced massive nasopharyngeal bleeding, presumably secondary to antiplatelet therapy and heparinization, resulting in airway compromise. Intubation was performed, but the patient’s respiratory status remained tenuous, necessitating complete sedation and high-rate, low-volume ventilation to maintain oxygenation. Despite repeated efforts, the patient was unable to be extubated and experienced progressive worsening of pulmonary function. He died 12 days after intervention.

### Discussion
Despite advancement in IA thrombolytic pharmacology and clot-retriever technology, recanalization rates >∼50% to 69%/4,13–15 have remained elusive. Many emboli are mature, fibrinous clots that are recalcitrant to thrombolytics. They may also adhere to the intima and become refractory to mechanical disruption or clot-retrieval. Moreover, thrombus may lodge within or extend from existing atheromatous disease, once again thwarting current revascularization efforts.

In addition to limited recanalization rates, current IA therapies, particularly IA thrombolytics, can take hours to achieve recanalization.16 Given the logical and literature-supported8–10 supposition that time-to-recanalization is crucial, rapid—and safe—recanalization is becoming a primary goal. However, the ideal method by which this rapid and safe recanalization is achieved is not clear.

Advantages of stent-assisted recanalization have become apparent in the setting of acute myocardial ischemia. Approximately 1 decade ago, stenting began to replace angioplasty as the primary means of revascularization for acute coronary syndrome.17–19 In 1 multicenter, randomized trial comparing stenting with angioplasty for acute MI, the mean minimal luminal diameter was larger after stenting than after angioplasty alone (P<0.001).20 Perhaps more importantly, the need for target-vessel revascularization because of ischemia was reduced in the stenting arm (7.7% vs 17.0%; P<0.001); the combined primary end point of death–reinfarction–disabling stroke–target-vessel revascularization was lower in the stent group (12.6 vs 20.1%; P<0.01). The trial concluded that stent implantation has clinical benefits beyond those of angioplasty alone for patients with acute MI. However, substantial differences exist in the pathophysiology of stroke vs MI, particularly regarding the typical etiology (embolic vs underlying stenosis) and vascular anatomy of these disease entities.

### Table. Brands, Dimensions, and Numbers of Self-Expanding Stents Deployed*

<table>
<thead>
<tr>
<th>Stent, mm</th>
<th>No. Deployed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wingspan 3.0×15</td>
<td>4</td>
</tr>
<tr>
<td>Wingspan 3.0×20</td>
<td>2</td>
</tr>
<tr>
<td>Wingspan 3.5×15</td>
<td>3</td>
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</tr>
<tr>
<td>Enterprise 4.5×12</td>
<td>1</td>
</tr>
<tr>
<td>Enterprise 4.5×22</td>
<td>1</td>
</tr>
</tbody>
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*One patient in this series did not receive a stent (details in text).
Nevertheless, these data certainly require consideration by the stroke-physician community.

Early support for mechanical displacement modalities for stroke treatment (of which stenting is one) as a contrast to clot removal modalities (such as Merci or Penumbra) can also be found in the angioplasty for stroke literature.21–24 These studies are among the first to our knowledge to discuss the possibility that clot removal is not, in itself, critical, but rather that recanalization should be the focus of intervention. Spring-boarding from these early experiences, the concept of stent placement for acute stroke became a serious consideration with the publication of 4 retrospective series9–11,25 and several case reports.26–29 In these series,9–11,25 recanalization rates of 79% to 92% were achieved after stent placement after other endovascular methods had failed. Although certainly encouraging, these studies were retrospective in nature and used stent deployment as a “salvage” technique and not the “first-line” tool.

In this prospective, Food and Drug Administration-approved, single-arm trial, we demonstrate that stent deployment appears to be a safe, technically feasible first-line method to achieve recanalization when treating acute ischemic stroke resulting from acute intracranial arterial occlusion. A primary stent-for-stroke approach resulted in a 100% recanalization rate (TIMI 3 = 60%, TIMI 2 = 40%). Previous prospective trials, such as the Interventional Management of Stroke II trial16 and the Multi-Mechanical Embolus Removal in Cerebral Ischemia trial,14 demonstrated recanalization rates of 64% and 70%, respectively. However, these data are not directly comparable because of contrasts in patient selection. Still, the results of this prospective single-arm trial are encouraging. It should be noted that adjuvant therapy after stent was occasionally used at the interventionist’s discretion. However, in 40% of cases no adjuvant therapies were used and, except for 1 case in which 4 mg of IA reteplase was used to treat a distal occlusion after recanalization, the remaining adjuvant-treated patients received some combination of eptifibatide or postdeployment angioplasty (among which 1 further patient also received IA-tPA administration). These treatments were supportive in nature to improve or maximize the partial recanalization that had already occurred. Although an ideal investigation would allow single modality assessment, ethical considerations require physician judgment regarding administration of adjuvant therapy. Interestingly, despite adjuvant IA antiplatelet therapy in 50% of patients, the symptomatic intracranial hemorrhage rate was only 5% and the asymptomatic intracranial hemorrhage rate was 10%. This compares favorably with symptomatic intracranial hemorrhage rates in previous stent-for-stroke series (11%–22%)10,11 and is in conjunction with more other accepted IA treatment modalities (~10%).15,16,30

At 1-month after intervention, 60% of patients had mRS scores ≤3 and 45% had mRS scores ≤1. These data are encouraging. Although caution must be taken in using reference data sets that are not truly comparable, these data do compare well to those for prospective trials such as Multi-Mechanical Embolus Removal in Cerebral Ischemia (36% of patients achieving mRS ≤2 at 90 days)15 and Interventional Management of Stroke II (46% of patients achieving mRS ≤2 at 3 months).16 The use of physiological imaging as a screening criteria, although unproven, may have improved patient selection and thus improved clinical outcomes, thereby further limiting the value of these reference trials for comparison. However, such a selection bias should not have significantly affected recanalization rate analysis, which provides additional support toward the overall value of a primary stent-for-stroke therapeutic option.

Mortality at 1 month was 25%. Although sobering, these results are within the range of reported mortality in other prospective stroke trials, such as Penumbra (1-month mortality=45%),30 Multi-Mechanical Embolus Removal in Cerebral Ischemia (3-month mortality=34%),15 and National Institute of Neurological Disorders and Stroke IV-tPA cohort (3-month mortality=21%).12 These trials had varied injury levels, with baseline NIHSS scores of 21 (mean), 19 (median), and 18 (mean), respectively. Therefore, the level of preprocedural deficit is higher in these previous cohorts and alternate mortality rates are not unexpected.

There are several limitations to this trial. Only 20 patients were enrolled, which by nature of its small number must limit the strength of any conclusions drawn. Additionally, there is only a single arm to this trial, and a randomized prospective trial will be required to adequately assess clinical efficacy. Last, because of the nature of the disease process, substantial heterogeneity exists among patients, further confounding interpretation and analysis.

These data appear to support the relative safety and angiographic efficacy of a primary stent-for-stroke treatment paradigm. Additionally, with highly encouraging 1-month clinical outcomes, these data seem to indicate the possibility of benefit in acute stroke treatment. It is crucial to stress the preliminary nature of these findings and, as such, further investigation will be required before any evidence-based conclusions can be generated. However, these data are sufficiently robust to provide impetus for continued investigation into a primary stent-for-stroke treatment paradigm.

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References
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