

Surgery and Neurointervention for Intracranial Atherosclerotic Steno-occlusive Disease

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Abstract

Neurosurgeons and neurointerventionists interested in cerebral revascularization to prevent stroke from intracranial atherosclerotic steno-occlusive disease were disappointed in 2011 with the closure of two important negative studies: the Carotid Occlusion Surgery Study (COSS) and Stenting and Aggressive Medical Therapy for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study. Debates are centered on what causes these failures. While extracranial-intracranial (EC-IC) bypass and neurointervention (angioplasty and/or stenting) cannot be considered a routine intervention for patients presenting with initial ischemic event in the setting of atherosclerotic steno-occlusive disease, selected patients with severe hemodynamic impairment and/or recurrent symptoms despite maximal medical therapy may still benefit from surgery and neurointervention at high-volume centers, which can offer the procedure with low peri-operative morbidity.

Keywords

Angioplasty, cerebral ischemia, EC-IC bypass, stenting, stroke

Disclosure: The authors have no conflicts of interest to declare.

Received: August 5, 2013 **Accepted:** October 31, 2013 **Citation:** *US Neurology*, 2014;10(1):56–60 DOI: 10.17925/USN.2014.10.01.56

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Surgery for Occlusive Atherosclerotic Disease

Extracranial-intracranial (EC-IC) bypass for revascularization in the setting of atherosclerotic occlusive disease has remained a topic of intense interest and scrutiny over the last 4 decades. The underlying premise of EC-IC bypass in this setting is to provide blood flow augmentation in the setting of cerebral ischemia, aiming to improve blood flow to oligemic brain tissue.

Evidence for Extracranial-Intracranial Bypass Anterior Circulation

In evaluating the efficacy of EC-IC bypass for ischemia, the primary focus has been on anterior circulation disease. Flow augmentation bypass in the anterior circulation primarily entails a bypass between the superficial temporal artery and the middle cerebral artery (STA-MCA). The EC-IC bypass study published in 1985 failed to demonstrate the efficacy of STA-MCA bypass over medical management in over 1,300 patients with occlusive disease of the anterior circulation.¹ Patients with transient ischemic attack (TIA) or stroke in the setting of occlusive disease not amenable to carotid endarterectomy (primarily carotid occlusion) were randomized to best medical therapy or best medical therapy in addition to EC-IC bypass. Although surgery was performed successfully, with a

reported bypass patency rate of 96 %, EC-IC bypass conferred no benefit in terms of stroke risk over the average follow-up period of 55.8 months.

Subsequent analysis of the study methodology identified shortcomings in study design and implementation that suggested universal abandonment of EC-IC bypass for ischemic was premature.^{2,3} The trial was criticized for potential selection bias in enrollment, with concerns that a large number of patients, more than enrolled within the study, actually underwent surgery outside the trial. This would suggest that patients may have been selectively offered surgery versus enrollment in the trial based on perceived benefit of intervention, thus diluting any beneficial effect of bypass in those within the study cohort. Concern was also raised regarding the adequacy of flow augmentation provided by the STA-MCA bypass, with the notion that higher flows through larger calibre bypass could be more effective. The STA-MCA bypass has been the primary type of bypass performed in the setting of ischemia, due to its high technical success rate and low morbidity given that anastomosis is performed to a distal cortical MCA branch with little risk for ischemia during cross-clamping.⁴ However, the degree of flow augmentation can be relatively modest compared with larger conduit bypasses such as vein or radial artery interposition grafts from the cervical carotid to the more proximal

MCA. Larger conduits do carry several disadvantages, however, including higher morbidity and lower patency rates,⁵ and the risk for ischemia during cross-clamping of the more proximal MCA. Additionally, there is concern for hyperperfusion hemorrhage when using high flow grafts to revascularize ischemic brain,⁶ presumed to be due to the inability of the vasodilated ischemic vascular bed to compensate acutely to a large increase in perfusion created by a high flow graft. Favorable preliminary results with higher flow grafts in small series have been reported with the use of a non-occlusive bypass technique, the excimer laser-assisted anastomosis (ELANA), which allows vein grafts to be placed onto large proximal vessels, such as the supraclinoid carotid artery or proximal MCA, without clamping the vessel during anastomosis.^{7,8} This technique is still under evaluation, but the lack of temporary vessel occlusion during surgery, or the more physiologic placement of the bypass proximally in the intracranial circulation, appears to reduce the risk for hyperperfusion.⁷

The most prominent drawback of the EC-IC bypass trial, which ultimately generated the most subsequent analysis and investigation, was the lack of hemodynamic evaluation in selecting patients for enrollment. In the trial, no objective physiologic criteria were used to assess cerebral blood flow, and thus patients may have presented with ischemic symptoms secondary to etiologies unlikely to benefit from bypass, such as embolic phenomena or small vessel disease. Subsequent to the EC-IC bypass trial, the role of hemodynamic assessment in evaluation of carotid occlusive disease has been extensively evaluated, demonstrating that hemodynamic evaluation can identify a subgroup at higher risk for recurrent stroke,^{9–15} and who would, therefore, be more appropriate candidates for revascularization. In the last 2 decades, two trials have attempted to address the efficacy of bypass in such patients with hemodynamic compromise. The Japanese EC-IC bypass trial (JET) randomized patients with symptomatic internal carotid artery (ICA) or MCA occlusive and hemodynamic impairment to undergo STA-MCA bypass versus medical therapy. Interim results based on analysis of 196 patients published in a Japanese language journal reported a favorable result for bypass at 2-year follow-up,¹⁶ with a reduced risk for the primary endpoint of death and stroke (23.1 % in the medical arm and 15.2 % in the surgical arm; $p=0.046$). The Carotid Occlusion Surgery Study (COSS) based in the US, however, did not support the efficacy of bypass for stroke-risk reduction.¹⁷

COSS enrolled patients with symptomatic carotid occlusion and hemodynamic impairment based on evidence of severe compromise on positron emission tomography (PET), which was considered to be more relevant than blood flow measurement alone.¹⁸ The study compared STA-MCA bypass with medical therapy alone, with a primary endpoint of ipsilateral ischemic stroke within 2 years, plus 30-day stroke and death. The study was prematurely halted in June 2010, after randomization of only 193 of the originally planned 372 patients. The termination of the study was based on futility analysis, as Kaplan-Meier estimates of the primary endpoint demonstrated essentially equivalent rates for the medical and surgical groups, at 23 % and 21 %, respectively. This occurred despite excellent graft patency rates and improvement in cerebral hemodynamics post bypass. The surgical group suffered a 30 day (peri-operative) event rate of 15 %, and despite a low subsequent stroke risk thereafter, failed to provide an overall benefit, given that the medical group actually demonstrated a much lower event rate than the 40 % stroke risk originally projected based on prior observational data.^{14,19} Based on

interim analysis, it was felt that a substantial increase in sample size from the originally anticipated 372 patients would be required to demonstrate any clinically meaningful difference in favor of surgery, and thus the study was terminated.

Although COSS was a carefully designed and well-executed study, several aspects of the study deserve further consideration.²⁰ The lower than anticipated stroke rate in the medical arm of the trial was largely attributed to improvements in medical therapy such as use of statins. However, the magnitude of the reduction approaches or exceeds that seen in trials of intensive active medical management,^{21,22} and raises the potential concern that the criteria for selection of highest-risk patients into the trial failed to do so as effectively as planned. The use of a semi-quantitative method for assessment of the hemodynamic compromise, based on relative right to left ratio, rather than the original absolute threshold utilized in earlier observational studies, has been raised as a potential concern in appropriately selecting the most compromised individuals.²³ Regardless, the surgical arm suffered a higher than desirable peri-operative event rate, at 15 %. Within the study, 30 surgeons performed the 93 bypasses,²⁴ which generally reflects the low-volume nature of this operation at any given site. A volume–outcome relationship has been well demonstrated in many aspects of cerebrovascular surgery, including EC-IC bypass, where the relationship has been found to be most robust when considering not only just individual surgeon caseload but also hospital volume. This may reflect the influence of epiphenomenon to the surgery including specialized nursing, anesthesia, and critical care in addition to the surgeon experience. If peri-operative event rates closer to 8 % had been achieved, surgery would have demonstrated clear benefit in the COSS population. It is worth noting that the stroke event rate after the 30-day peri-operative period was significantly lower in the bypass patients at 9 % compared with 22.7 % in the medical group. In conjunction with the hemodynamic improvement seen on PET in the surgical patients, these data do seem to confirm the general concept that revascularization is beneficial, but only if it can be performed with low enough surgical risk. Even with the current rates reported in COSS, if stroke rates were to remain steady in both groups beyond the 2-year follow-up, the Kaplan-Meier curves would cross over to a significant benefit of surgery at about 5 years. One other important consideration when interpreting the results of COSS is the recognition that hemodynamically unstable patients, although a small subgroup of patients with carotid occlusion, were not well represented in the study population. The mean time to enrollment within COSS was 72 days, and thus likely represented more stable patients.

In conjunction with COSS, an ancillary study, Randomized Evaluation of Carotid Occlusion and Neurocognition (RECON), followed a subset of patients to examine cognitive outcomes. The results have not yet been published, but preliminary presentation of the data at the International Stroke Conference 2013 indicated that no cognitive benefit was realized in the small cohort studied. There has been prior non-randomized data supporting improvement of cognitive function, post bypass^{25,26} and even the interesting notion of functional benefits, such as increased brain volume and improvement in fixed neurologic deficits.^{27–29} Such preliminary data will require further investigations.

After recent publication of the technical aspect of the COSS,²⁴ several concerns have also been voiced from Japanese vascular neurosurgeons.

First, the duration of MCA occlusion in the study might have been too long: in patients who developed ischemic stroke, the average occlusion time was 55.9 minutes.²⁴ Even in those who did not develop stroke, the duration was 45.4 minutes.²⁴ Experienced Japanese neurosurgeons who routinely perform EC-IC bypass procedures typically report completing suturing of the STA to the MCA within 30 minutes of occlusion time.^{30,31} Although the list of participants in the COSS trial included many expert vascular neurosurgeons, the longer average occlusion times may reflect the relative rarity of EC-IC bypass procedures in the US. Although occlusion times in COSS were not linked to risk for peri-operative stroke *per se*, there is lingering concern that this may have been a contributory factor. Additionally, a single anastomosis was performed in COSS patients,²⁴ which may provide insufficient blood flow to the ischemic area. Although elevated oxygen extraction fraction (OEF) was markedly improved post bypass; it did not normalize. By contrast, it is the Japanese practice to create a double anastomosis to the frontal and temporal branches of the middle cerebral artery.^{30,31} However, consideration should be made about possible mentioned increased risk for hyperperfusion syndrome and risk for skin necrosis and the fact that single bypass usually tends to increase flow volume during long follow-up. Moreover, the frontal branch may be within the collateral system of the occluded ICA via the ophthalmic artery. Second, there has been little description in the published study of how patients were managed post-operatively, except that they received oral aspirin.^{17,24} Japanese neurosurgeons are well aware that strict blood pressure control is essential for patients who undergo EC-IC bypass, since the incidence of hyperperfusion syndrome may not be rare.^{30,31} The use of near-infrared spectroscopy both for surgery and for non-invasive bedside measurement of regional cerebral oxygenation seems to be useful in the early detection of hyperperfusion syndrome.³¹ Interestingly, the great majority of reports on hyperperfusion syndrome have come from Asian countries,^{30,31} and it is uncertain whether the potential risk for hyperperfusion syndrome had been fully recognized by the neurocritical care physicians participating in COSS. Japanese neurosurgeons also have to do more: although positive results for the surgical treatment have been obtained from the JET study, it has still not been published in peer-reviewed English-language journal at the time of writing,¹⁶ even though more than 10 years have passed after completion of the JET study. Medical treatment has improved significantly during that period, and new data would be required to convincingly demonstrate to neurologists, neurosurgeons, and patients worldwide that EC-IC bypass surgery is truly efficacious and safe.

Posterior Circulation

Data regarding bypass for posterior circulation ischemia are sparse. This likely reflects the relative prevalence of the condition, and the emergence of less-invasive endovascular techniques in the face of the relative higher morbidity and technical complexity of posterior circulation bypass.^{32,33} Furthermore, objective assessment of hemodynamic compromise in the posterior circulation has generally been more difficult: the imaging methods used in evaluation of anterior circulation ischemia are less useful in assessment of the posterior circulation,³⁴ due to the more compact brain territory and skull base artefacts. An alternative method for assessing posterior circulation blood flow relies on large vessel flow measurement using quantitative magnetic resonance angiography (QMRA), a technique utilizing phase contrast MR to measure vessel specific volumetric flow rates. Preliminary results from patients with

vertebrobasilar occlusive disease have shown that QMRA can identify patients with flow compromise, a group at higher risk for recurrent stroke.³⁵ The utility of this imaging in identifying high-risk patients is currently under investigation in prospective fashion.³⁶

Bypass operations utilizing a variety of donor and recipient vessels have been described for the posterior circulation, including occipital artery (OA) to posterior inferior cerebellar artery (PICA), STA to posterior cerebral artery (PCA) and STA to superior cerebellar artery (SCA) bypasses. Overall, these carry higher risk and lower patency rates than those seen with anterior circulation STA-MCA bypass. Patency rates for OA-PICA bypass range from 88 to 100 %, with mortality averaging 4 %;³² STA-PCA and STA-SCA bypasses carry a 78–90 % patency rate, with mortality averaging 12 %^{32,33} and serious morbidity of 20 %. Although these series report improvement in a subset of patients, the morbidity and mortality have introduced caution when considering bypass, particularly in patients with poor neurologic condition or medical co-morbidities. Consequently, EC-IC bypass is performed rarely in this situation, and on a case-by-case basis reserved for the infrequent situation when symptoms are refractory to maximal medical therapy, hemodynamic compromise is demonstrable and the disease is not amenable to endovascular interventions.

Current Indications for Extracranial-Intracranial Bypass

Following publication of the original EC-IC bypass trial, surgical revascularization with bypass in the setting of atherosclerotic disease has become increasingly restricted to a small, and select, population of patients who experience refractory symptoms despite maximal medical therapy.^{37,38} With the more recent trial data, EC-IC bypass cannot be considered a routine procedure for patients presenting with initial ischemic event in the setting of atherosclerotic occlusive disease. However, selected patients with severe hemodynamic impairment and/or recurrent symptoms despite maximal medical therapy could benefit from surgery at high-volume centers that offer the procedure with low peri-operative morbidity.

Angioplasty and Stenting for Intracranial Atherosclerotic Stenosis

Intracranial atherosclerotic stenosis is a cause of 8 to 10 % of cases of ischemic stroke in the US and up to 33 % of ischemic strokes in Asia, respectively.^{39–41} The annual risk for stroke from all causes in patients with intracranial atherosclerosis is estimated to be 3.6 % to 13 %.^{42–49} Angioplasty and/or stenting are advocated to improve cerebral blood flow and stabilize vulnerable plaque, with a goal to prevent recurrent stroke in patients with symptomatic and severe intracranial stenosis.⁵⁰

Evidence for Angioplasty and Stenting

Favorable results using self-expanding stents aroused interest and subsequently initiated studies into neurointerventional treatment of intracranial atherosclerotic stenosis worldwide.⁵¹ The risk for major peri-procedural complication as represented by stroke or death at 30 days following intracranial stenosis using Wingspan varied from 4.5 % to 9.6 % in the early studies.^{51–53} Over a mean imaging follow-up time of 8.5 months, the incidence of in-stent restenosis (ISR) following Wingspan was reported to be 28.3 % (36/127), with 3.9 % (5/127) evolving into complete stent occlusion: a third of them were symptomatic.⁵⁴

Stenting and Aggressive Medical Therapy for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) was an investigator-initiated randomized, controlled, multi-center clinical trial to test whether early angioplasty and stenting can reduce subsequent ischemic stroke risk in patients with symptomatic severe stenosis of a major intracranial artery.⁵⁵ Medical management in SAMMPRIS was identical in the two groups and consisted of aspirin, at a dose of 325 mg per day; clopidogrel, at a dose of 75 mg per day for 90 days after enrollment; management of the primary risk factors (elevated systolic blood pressure and elevated low-density lipoprotein [LDL] cholesterol levels), and management of secondary risk factors (diabetes, elevated non-high-density lipoprotein [non-HDL] cholesterol levels, smoking, excess weight, and insufficient exercise) were achieved with the help of an intensive medical regimen and a lifestyle modification program. It was found that angioplasty and stenting was inferior to aggressive medical therapy in prevention of recurrent stroke in patients with intracranial atherosclerotic stenosis. The peri-procedural stroke or death rate within 30 days after Wingspan stenting (14.7 %) in SAMMPRIS was substantially higher than the rates reported in earlier case series.^{51–53}

The high rate of peri-procedural complication was attributed to inclusion of patients with recent symptoms that could lead to increased risk for distal embolism during stenting.^{56,57} Peri-procedural complications in SAMMPRIS were mainly due to ischemic stroke (63.3 %, 19/30), which was largely due to perforator stroke (63.1 %, 12/19), and others such as embolic, mixed perforator and embolic, and stent occlusion. The other peri-procedural complications were due to hemorrhagic stroke, which was either subarachnoid hemorrhage (45.5 %, 5/11) or intracerebral hemorrhage (IC) (54.5 %, 6/11). The majority (83.3 %, 5/6) of IC presented ≥ 4 hours after stenting. All cases of fatal hemorrhage were due to IC.⁵⁸

The importance of a learning curve factor in intracranial stenting has been highlighted subsequently. A low peri-procedural complication rate of 5 % was reported in a prospective study of 100 consecutive cases

performed in China,⁵⁹ and the low complication rate was attributed to the experience of the two operators, who had prior experience of more than 180 procedures of intracranial stenting.⁶⁰ A learning curve seems to be necessary for mastering Wingspan stenting for intracranial atherosclerosis and preventing peri-procedural complications from occurring.

Another study from Hong Kong confirmed that the peri-procedural complication rate could be lower (5.3 %, 3/57) when the procedures were performed in a referral center by a constant team of operators.⁶¹ The incidence of ISR at 1-year follow-up with digital subtraction angiography (DSA) in this Hong Kong study was 16.7 % (11/66),⁶² and all were asymptomatic. In subsequent radiologic follow-up, luminal gain beyond baseline diameter was observed in 36 lesions (54.5 %).⁶²

Alternatives to self-expanding stents have also attracted attention recently. There is a revival of interest in primary balloon angioplasty.⁶³ Additionally, a 182-patient series of balloon-expandable stents in intracranial atherosclerotic disease was recently reported.⁶⁴ Technical success was achieved in 97 % and the incidence of stroke at 30 days was 5.6 %. The 1-year incidence of all strokes or TIAs (including periprocedural) in this study was 18 (9.8 %), and all these symptomatic patients were advised to continue dual antiplatelets lifelong.

Current Indications for Angioplasty and Stenting

With the results of SAMMPRIS, angioplasty and stenting with self-expandable stents should not be employed for first-time acute ischemic stroke related to intracranial atherosclerotic stenosis. Acceptable 30-day stroke and mortality rate may be achievable in carefully selected patients with recurrent stroke related to intracranial atherosclerotic stenosis and refractory to medical treatment. Whether a certain subgroup may benefit more from neurointervention should be further investigated.⁶⁵ Different techniques such as primary balloon angioplasty, balloon expandable stents, drug-eluting balloon, and stents should be further assessed in future comparative effectiveness studies. ■

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