Extracranial-intracranial bypass for ischemic cerebrovascular disease: what have we learned from the Carotid Occlusion Surgery Study?

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Extracranial-intracranial (EC-IC) arterial bypass has been used in the treatment of various neurosurgical pathologies including skull base tumors requiring sacrifice of a large intracranial artery; complex intracranial aneurysms requiring trapping; and distal revascularization, moyamoya disease, and symptomatic cerebrovascular stenoocclusive disease. The latter indication has been the subject of intense investigations in several large randomized controlled trials, most recently the Carotid Occlusion Surgery Study (COSS). In the present literature review and synthesis, the authors examine the current evidence available for EC-IC arterial bypass for the treatment of ischemic cerebrovascular disease including both extracranial carotid artery occlusive disease and intracranial atherosclerotic disease. They focus particular attention on EC-IC arterial bypass for the treatment of symptomatic hemodynamic cerebral ischemia and how lessons learned from the COSS might guide future investigations into the treatment of this disease.

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Ischemic cerebrovascular disease is a broad term referring to a wide variety of conditions that cause ischemic stroke or transient ischemic attack (TIA). For this review, we focused on the following 2 major categories of ischemic cerebrovascular disease: 1) extracranial atherosclerotic internal carotid artery (ICA) occlusion, in which the extracranial ICA alone or in combination with the intracranial ICA is occluded due to atherosclerotic disease with or without superimposed thrombus, and 2) large-artery intracranial atherosclerotic disease (ICAD), in which one or more major intracranial arteries (for example, the ICA and/or middle cerebral artery [MCA]) are stenosed or occluded due to atherosclerotic disease. Complete carotid artery occlusion causes approximately 10% of TIA and 15%–25% of ischemic strokes in the carotid artery territory.16,30 The 2-year risk of subsequent ipsilateral ischemic stroke—in the context of best medical therapy—has been estimated at 10%–15%.16,19,30 Intracranial atherosclerotic disease accounts for approximately 9% of all ischemic strokes in the United States,37 resulting in approximately 65,000 strokes per year with a 2-year recurrence risk of 15%–20%.7,27

Given the high rate of recurrent ischemic events in both of these patient populations,9,11 surgical revascularization has been used as a potential treatment option. Extracranial-intracranial (EC-IC) bypass performed in patients with cerebral ischemia has usually been a superficial temporal artery (STA)–middle cerebral artery (MCA) cortical branch anastomosis. In this review, the authors will examine the historical background and existing evidence for the use of STA-MCA bypass in patients with ischemic cerebrovascular disease and provide a perspective on the future of EC-IC bypass for ischemic cerebrovascular disease and ways that it might be performed more safely and, therefore, potentially more effectively in this patient population.

Extracranial-Intracranial Bypass for Extracranial Atherosclerotic ICA Occlusion

Historical Background and Existing Evidence

In 1965, Gazi Yaşargil, working with R. M. Peardon Donaghy in the microsurgical laboratory at the University of Vermont, performed an anastomosis between the STA and a branch of the MCA in a canine.49 The first
clinical application of the procedure, an STA-MCA cortical branch anastomosis, was independently performed by Yaşargil in Zurich, Switzerland, on October 30, 1967, and on the following day by Donaghy at the University of Vermont. Shortly after the development of the EC-IC arterial bypass, the procedure became widely used for the treatment of ischemic cerebrovascular disease including that in patients with symptomatic ICA occlusion. In the 1970s and early 1980s, multiple small retrospective case series documented the safety record and apparent efficacy of this procedure. While the majority of these studies included patients with heterogeneous disease processes (for example, intracranial anterior circulation stenosis, intracranial posterior circulation stenosis, extracranial ICA stenoocclusion, moyamoya disease, and ICA dissection), the minority focused on patients with symptomatic extracranial ICA occlusion.

Retrospective Case Series of EC-IC Bypass for Ischemic Cerebrovascular Disease

In 1985, Sundt and colleagues reported their series of 415 patients who underwent STA-MCA cortical branch anastomosis over an 8-year period for ischemic cerebrovascular disease. In this surgical cohort, the authors observed a bypass graft patency rate of 99% (determined by either cerebral catheter angiography or Doppler ultrasonography). The same group later reported an STA-MCA graft patency rate of 96% (via cerebral angiography) in a separate analysis of 157 of these patients with complete extracranial ICA occlusion. In addition to these studies, other case series have documented EC-IC bypass graft patency rates between 90% and 96%.4,5,29,38,40

In 1978, a literature review examining multiple case series of STA-MCA bypass procedures (376 total operations) reported a permanent neurological morbidity rate of 2.4%, an operative mortality rate of 4.3%, and an “other morbidity” rate of 13.6%. Other surgical case series (from the same time period) that included between 100 and 415 patients undergoing STA-MCA bypass operations reported perioperative ischemic stroke rates and mortality rates of 2%-3.6% and 1.2%-3%, respectively. In a more recent series of 47 patients undergoing STA-MCA cortical branch anastomosis for symptomatic extracranial ICA occlusion, they observed a 3% perioperative ischemic stroke rate and a 0% perioperative mortality rate.

International EC-IC Bypass Trial

Published in 1985, this prospective randomized trial investigated whether EC-IC arterial bypass, in addition to best medical therapy, was superior to best medical therapy alone in patients with ischemic cerebrovascular disease including extracranial ICA occlusion. The study included 1377 eligible patients who experienced one or more TIAs or minor ischemic strokes within 3 months of enrollment and demonstrated evidence of 1) stenosis or occlusion of the MCA proximal trunk, 2) stenosis of the ICA above the C-2 vertebral body (for example, inaccessible to carotid endarterectomy), or 3) extracranial atherosclerotic ICA occlusion. The average follow-up duration was 55.8 months, during which 99% of medically treated patients experienced one or more strokes compared with 31% in the surgical group (no significant difference). The study results showed a bypass patency rate of 96%, 30-day perioperative stroke rate of 12.2% for cerebral or retinal ischemic events ranging from “trifling symptoms to fatal strokes,” major stroke rate of 4.5%, and perioperative mortality rate of 1.1%. The incidence of fatal and nonfatal ischemic strokes was not significantly different in patients randomized to EC-IC arterial bypass versus those patients randomized to medical therapy alone. When data in patients with extracranial ICA occlusion were analyzed separately, similar results were noted. Specifically, the rate of fatal and nonfatal strokes in ICA occlusion patients who had continued ischemic symptoms between the time of randomization and surgery was also not significantly different in those in the surgery arm compared to those in the medical arm. Moreover, no trend toward surgical benefit was found in patients with “stable” extracranial ICA occlusion (for example, those patients who did not experience symptoms between randomization and surgery). These strongly negative results led to a widespread reduction in EC-IC bypass surgery for patients with ischemic cerebrovascular disease, including those with extracranial ICA occlusion.

The results of the EC-IC Bypass Trial were met with multiple criticisms. Among these was, first, that the STA donor artery was a relatively low-flow vessel and did not afford adequate revascularization compared with a high-flow donor artery (for example, the radial artery or saphenous vein graft from the cervical carotid artery to the MCA branch). This criticism was likely invalid given that multiple groups have reported that STA-MCA cortical branch anastomosis can reverse an abnormally elevated oxygen extraction fraction (OEF). Second, many of the highest-risk patients may have been operated on outside of the trial and, therefore, not included in the study results, leading to a selection bias. This claim was conclusively refuted by further data provided by the EC-IC Bypass Trial Investigators. Third, critics noted that no hemodynamic criteria were used to select those high-risk patients who were most likely to benefit from revascularization. This latter criticism was particularly germane given that ICA occlusion does not always predict cerebral hemodynamic impairment in individual patients. This key issue formed the basis for the St. Louis Carotid Occlusion Study (STLCOS) and, subsequently, COSS.

Stages of Cerebral Hemodynamic Impairment

Complete ICA occlusion may precipitate a reduction in cerebral perfusion pressure (CPP) in the distal cerebral circulation, depending on the extent of extracerebral and cerebral collaterals. When CPP is reduced, near-instantaneous compensatory changes in the cerebrovascular circulation occur in an effort to maintain cerebral metabolism. The most notable of these changes are 1) autoregulatory cerebral vasodilation and 2) an increase in...
the amount of oxygen extracted from the blood (OEF).\textsuperscript{34} If CPP drops after ICA occlusion due to lack of adequate collaterals, the CBF and cerebral metabolic rate may be maintained solely via cerebral autoregulatory vasodilation. This is considered Stage I hemodynamic failure and is typified by reduced arterial response to vasodilatory stimuli (decreased cerebrovascular reserve) and normal OEF.\textsuperscript{19} If CPP drops even further after ICA occlusion such that cerebral autoregulatory capacity is exhausted and CBF is reduced, the cerebral metabolic rate can be maintained by an increase in OEF. This is considered Stage II hemodynamic failure, or “misery perfusion,” and is characterized by a loss of cerebrovascular reserve and an increase in OEF.\textsuperscript{19,34} If CPP is reduced to the point that both cerebral autoregulatory vasodilation and increased OEF compensatory mechanisms are depleted, however, cerebral metabolic rate cannot be maintained and Stage III failure or “true ischemia” occurs.

Subsequent to the International EC-IC Bypass Trial, the evolution of modern imaging techniques made it feasible to assess these stages of hemodynamic impairment in patients with ischemic cerebrovascular disease. To identify Stage I hemodynamic failure, paired CBF measurement techniques are typically employed. This involves acquisition of an initial CBF measurement at rest and a subsequent CBF measurement after a vasodilatory stimulus (for example, acetazolamide, hypercapnia, and hand movements).\textsuperscript{14} When the normal CBF increase is reduced or absent after the vasodilatory stimulus, this indicates that the patient has impaired cerebrovascular reserve and is at Stage I hemodynamic impairment (at minimum). Modalities used to obtain this CBF measurement include Xe CT, SPECT, PET, and MRI. Alternatively, resting-state cerebral blood volume assessed using MRI, PET, or SPECT can be used as an indirect measure of cerebral autoregulatory vasodilation.\textsuperscript{19} To identify Stage II hemodynamic failure, OEF must be calculated. This is only accurately accomplished via PET-based analyses. While patients with Stage I and Stage II hemodynamic failure have both been identified as being high risk for subsequent ischemic events, the most robust data regarding the impact of impaired hemodynamics on subsequent risk come from prospective studies utilizing PET to identify patients with Stage II hemodynamic failure.

\textit{St. Louis Carotid Occlusion Study}

Grubb et al.\textsuperscript{19} tested the hypothesis that Stage II hemodynamic failure (as measured by increased OEF on PET) distal to a symptomatic extracranial ICA occlusion was an independent risk factor for subsequent ischemic stroke in medically treated patients. This study was a blinded, prospective, longitudinal cohort study of 81 patients with previous stroke or TIA in the territory of an occluded ICA. The authors found that the risk of all stroke and ipsilateral ischemic stroke in symptomatic subjects with increased OEF was significantly higher than in those patients with normal OEF (p = 0.005 and 0.004, respectively).\textsuperscript{19} The age-adjusted relative risk conferred by increased OEF was 6.0 (95% CI 1.7–21.6) for all stroke and 7.3 (95% CI 1.6–33.4) for ipsilateral stroke. Univariate and multivariate analyses of numerous baseline patient risk factors confirmed the independence of this relationship.

The STLCOS conclusively demonstrated that symptomatic patients with extracranial ICA occlusion were at increased risk of subsequent ischemic stroke. Importantly, previous studies had established that EC-IC bypass surgery could improve hemispheric OEF ratios in Stage II patients back toward normal levels.\textsuperscript{6,17,33,39} Therefore, despite the negative results of the EC-IC Bypass Trial, the STLCOS set the stage for a randomized controlled trial with a reliable method for identifying patients in whom cerebral hemodynamic factors were of primary pathophysiological importance.

Other investigators also examined OEF on PET as a predictor of subsequent ischemic stroke. For example, Yamauchi et al.\textsuperscript{48} prospectively evaluated 40 patients with symptomatic ICA occlusion (n = 30) or MCA occlusion (n = 10) over 5 years. They observed that patients with elevated OEF were at increased risk of all stroke (5 of 7 patients with increased OEF vs 6 of 33 patients with normal OEF; p < 0.0002) and ipsilateral ischemic stroke (4 of 7 patients with elevated OEF vs 5 of 33 patients with normal OEF; p < 0.0018). Also, they found that elevated OEF significantly increased subsequent stroke recurrence (RR = 7.2 for all stroke [p < 0.005] and RR = 6.4 for ipsilateral stroke [p < 0.01]). These results helped validate the importance of OEF as an independent predictor of ischemic stroke in patients with extracranial ICA occlusion.

\textit{Carotid Occlusion Surgery Study}

The COSS was a prospective, parallel-group, 1:1 randomized, open-label, blinded-adjudication treatment trial designed to test the hypothesis that STA-MCA cortical branch anastomosis—added to best medical therapy—would reduce the 2-year risk of subsequent ipsilateral ischemic stroke by 40% in patients with carotid occlusion and recently symptomatic cerebral ischemia.\textsuperscript{32} Patients with angiographically proven ICA occlusion causing an ischemic stroke or TIA within 120 days and hemodynamic cerebral ischemia (indicated by an increased OEF ratio on PET) were randomized to best medical therapy or best medical therapy plus STA-MCA bypass. One hundred ninety-five patients were randomized: 97 to the surgical group and 98 to the medical group. The study was halted prematurely due to futility. In the intention-to-treat analysis, the 2-year rates for ipsilateral stroke were 21% for the surgical group and 22.7% for the medical group (p = 0.78).\textsuperscript{32} Perioperative (within 30 days of surgery) ipsilateral stroke rates were 14.4% in the surgical group and 2.0% in the medical group, a significant difference of 12.4% (95% CI 4.9%–19.9%). The study concluded that EC-IC bypass surgery in this patient population was not of clinical benefit.

A subsequent paper detailed the surgical results of COSS. In that study, Grubb et al.\textsuperscript{20} reported that the surgical group exhibited high rates of bypass graft patency (98% at the 30-day postoperative visit and 96% at the last follow-up examination), improved cerebral hemodynamics as measured by OEF on PET, and much lower rates of recurrent ipsilateral ischemic stroke after postoperative Day 2 compared with the medical group (9% vs 22.7%,
This report was followed by a post hoc qualitative analysis of the mechanisms of perioperative ischemic stroke in the COSS surgical cohort. In this investigation, Reynolds et al. retrospective identified patients from the COSS with an ipsilateral perioperative ischemic stroke and categorized stroke mechanisms as bypass graft related (ischemic infarct in the territory of the recipient artery, likely related to technical performance of the anastomosis) or non–bypass graft related (ischemic infarct attributable to embolism, hypoperfusion, or other cause). The vast majority of perioperative ischemic strokes (86% or 12 of 14) were found to be unrelated to performance of bypass grafting, while the minority (21.4% or 3 of 14) were found to be related to performance of bypass grafting. One patient was considered to have dual stroke mechanisms. The authors concluded that the majority of ischemic strokes were not attributable to technical problems with the anastomosis but were most likely due to the hemodynamic fragility of the patient population involved.

The COSS encountered several criticisms following its publication in 2011. Each of these criticisms has been thoroughly refuted in previous reports and will not be reiterated here.

**Japanese EC-IC Bypass Trial**

Similar to COSS, the Japanese EC-IC Bypass Trial (JET) was a multicenter, randomized controlled trial designed to test the hypothesis that STA-MCA cortical branch anastomosis, in addition to best medical therapy, could significantly reduce subsequent ischemic events in patients with recently symptomatic hemodynamic cerebral ischemia from chronic occlusive lesions of the ICA or MCA. Hemodynamic cerebral ischemia was determined by measuring MCA perfusion at rest and, following acetazolamide administration, with 3D quantitative blood flow measurements (for example, PET, SPECT, or Xe CT). These patients with at least Stage I hemodynamic impairment were randomized to receive surgery plus medical therapy or medical therapy alone. Patient randomization was further dichotomized based on hemodynamic response to acetazolamide (for example, moderate or severe cerebral ischemia).

Based on the JET interim analysis, 196 individuals were enrolled into the study; 98 patients were randomized to receive medical therapy in addition to EC-IC bypass, while 98 patients were randomized to receive medical therapy alone. Prior to randomization, cerebral ischemia was documented as moderate in 104 patients and severe in 92 patients. Overall, surgical patients experienced a significant reduction in the study’s primary end point (major stroke or death in the 2-year period after surgery) as compared with the medical patients with a mean follow-up period of 15 months (3.1% vs 14.3%, respectively; p = 0.046). Examination of the published Kaplan-Meier curves from the second interim analysis of JET shows no end points within the 1st month in the surgical group. There is no explicit mention whether the results include the 30-day postoperative morbidity and mortality rate, but it seems unlikely that this rate was 0 given that it was 12% in the original EC-IC bypass trial and 15% in COSS. We are not aware of publication of the final JET results.

**Extracranial-Intracranial Bypass for ICAD**

**Historical Background and Existing Evidence**

Symptomatic ICAD portends a high rate of recurrent, disabling ischemic strokes. In fact, several large clinical trials have documented recurrence rates of 14%–19% over 2 years, with the majority of events occurring in the 1st year. In the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study—a retrospective, multicenter trial that compared the efficacy of warfarin with aspirin for the prevention of major vascular events—73% of patients with recurrent strokes had ischemic lesions in the territory of the symptomatic artery. One recent clinical trial—Stenting versus Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS)—also demonstrated that in patients with symptomatic ICAD, best medical therapy was superior to angioplasty and stenting. Therefore, given the high rate of recurrent strokes in the territory of a stenotic intracranial artery on best medical therapy alone and the lack of benefit of current endovascular strategies, surgical revascularization could be considered as a treatment option.

In the mid-1980s, Weinstein et al. reported on the surgical results of EC-IC bypass in patients exclusively with symptomatic ICAD. In their series of 105 patients, they observed a graft patency rate of 97% with a perioperative morbidity and mortality rates of 2.8% and 1%, respectively. For long-term outcomes, they observed a late-onset stroke rate of 1.5% per year, a rate that was favorable compared with the natural history of medically treated patients. More recently, Tsai and colleagues reported on a series of 11 patients who underwent EC-IC arterial bypass for symptomatic ICAD related to MCA stenosis or occlusion. They observed a bypass graft patency rate of 100% with perioperative morbidity and mortality rates of 0% and 0%, respectively. The rate of ischemic stroke in long-term follow-up was not documented in this report. Andrews et al. performed STA-MCA arterial bypass procedures in 65 patients with ICAD (47 with MCA stenosis and 18 with MCA occlusion) and a history of recent TIA or ischemic stroke. They observed a perioperative ischemic stroke rate of 4.3% in the MCA stenosis group and 0% in the MCA occlusion group. The TIIAs completely resolved in 90% of MCA stenosis patients and in 92% of MCA occlusion patients. There were no perioperative deaths due to stroke in either group. The bypass graft patency rate was 100% at late follow-up. Whisnant and colleagues reported on their series of 239 patients who underwent STA-MCA bypass for the indications of TIA, mild ischemic stroke, or transient monocular visual symptoms. Notably, 82 of these patients had ICAD (either carotid siphon stenosis or MCA stenosis/occlusion). After bypass, the rate of ischemic stroke was 2.5% per year on an actuarial basis. The 30-day perioperative ischemic stroke rate was 3.3% and the perioperative mortality rate was 0%. The authors did not observe a reduction in the
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annual ischemic stroke rate in the postsurgical group compared with a nonsurgical cohort with ischemic symptoms related to proven ICA occlusion. Based on these retrospective case series, EC-IC surgical bypass was accepted as a viable treatment modality for patients with symptomatic carotid artery occlusion and ICAD.

International EC-IC Bypass Trial

The benchmark International Cooperative EC-IC Bypass Trial remains the largest, prospective, third-party adjudicated study to examine the safety and efficacy of EC-IC bypass for patients with ischemic cerebrovascular disease, including symptomatic ICAD. In this study, approximately one-third of enrolled patients had symptomatic ICAD. As mentioned above, the overall incidence of fatal and nonfatal ischemic strokes was not significantly different in those patients randomized to EC-IC bypass versus those patients randomized to medical therapy alone. When data in patients with symptomatic ICAD were analyzed separately, similar results were noted, particularly in those with intracranial stenosis rather than complete arterial occlusion. In patients with severe inaccessible ICA stenosis or MCA occlusion, no significant difference in the primary end point was noted between the medical and surgical groups. In patients with severe MCA stenosis, those in the surgical group fared significantly worse than those in the medical group. It is hypothesized that this apparent harm was likely secondary to post-bypass stasis at the stenotic MCA segment due to competing antegrade flow in the native artery and retrograde flow in the arterial bypass, leading to thromboembolic sequelae. Though no cerebral hemodynamic testing was performed in any of the patients with symptomatic ICAD in International EC-IC Bypass Trial, it seems unlikely that identifying a subgroup of ICAD patients with significant hemodynamic impairment would afford a superior surgical outcome given the results of COSS.

Discussion

The COSS was the clinical culmination of over 3 decades of intense efforts to determine whether EC-IC arterial bypass afforded clinical benefit to a subgroup of patients with symptomatic ICA occlusion and significant hemodynamic impairment. While well conducted, well controlled, and adequately powered, this trial did not show a clinical benefit for EC-IC bypass surgery. The as expected high risk of perioperative ischemic stroke and the as expected benefits of surgery were not sufficient to counterbalance the better than expected outcomes for the medical cohort.22 High rates of bypass graft patency were achieved,20,32 and the technical performance of the cortical branch anastomoses was excellent, as evidenced by the small number of perioperative ischemic infarcts in the recipient artery territory.26 The COSS confirmed the ability of EC-IC bypass surgery to improve hemodynamics and proved that successful improvement of OEF greatly reduces the risk of subsequent stroke in these patients. The preponderance of evidence from COSS suggests that patients with ICA occlusion and recently symptomatic cerebral ischemia that meet the inclusion/exclusion criteria defined in the trial are likely hemodynamically tenuous and unable to tolerate a surgery of this nature.20,52,56

Taken together, COSS and the International EC-IC Bypass Trial have provided Level I evidence for the contraindication of EC-IC bypass in patients with recently symptomatic extracranial ICA occlusion with or without evidence of Stage II hemodynamic failure on PET (COSS). Similarly, the International EC-IC Bypass Trial indicates that EC-IC bypass is not indicated for most patients with intracranial ICA or MCA stenosis or occlusion (that is, surgery is likely not helpful). Pilot studies examining indirect surgical techniques (for example, endovascular treatment) in patients with ischemic cerebrovascular disease and impaired cerebral hemodynamics suggest that less invasive approaches toward achieving surgical revascularization are similarly ineffective and therefore not likely indicated.25 However, as with all clinical trials, there always, at least theoretically, may exist highly select subgroups of patients who were not specifically analyzed in the aforementioned trials. Such subgroups may be postulated and may serve as the basis for future trials, as was done for those with hemodynamic ischemia and COSS. However, until such trials are done, the theoretical existence of such subgroups is not justification for surgical treatment. Here, we will comment on some subgroups that might serve as a basis for further trials but for which the current evidence documented in the patients studied in the EC-IC Bypass Trial and COSS does not support the efficacy of surgery.

First, patients with debilitating orthostatic hypoperfusion syndrome, or “limb-shaking TIsAs,” were a subgroup not specifically examined in COSS. Second, patients with recently symptomatic ICA occlusion and with particularly severe hemodynamic impairment (very high OEF documented on PET) may represent a distinct subgroup that is at even higher risk for ischemic stroke and, therefore, might benefit from revascularization surgery (presuming their risk from surgery is not significantly higher). Third, patients with chronic retinal ischemia resulting in progressive visual loss were excluded from COSS and might benefit from EC-IC bypass if perioperative morbidity is sufficiently low. For EC-IC bypass to be beneficial in any of these or any other subgroups, the perioperative risk achieved in another randomized trial would have to be much lower than that achieved in COSS and the International EC-IC Bypass Trial. Therefore, novel methods or approaches to reduce perioperative ischemic complications should be explored as a means of improving the efficacy of EC-IC bypass. One approach could be the administration of a neuroprotective agent during the surgical bypass. Evidence supporting this concept comes from a recent investigation examining the benefit of preoperative administration of the neuroprotective drug NA-1 (an inhibitor of the postsynaptic density 95 [PSD-95] protein) to patients undergoing endovascular coiling of ruptured or unruptured intracranial aneurysms. The authors found that patients receiving the drug (n = 93) sustained fewer ischemic infarcts than did patients receiving a placebo (n = 93), as measured by diffusion-weighted MRI.25 A second approach could be employing a less-invasive and lower-risk revascularization procedure—for example, endovascular recanalization. This approach has
been successfully applied to patients with subacute to chronic stage ICA occlusion in several small case series with reported low rates of perioperative morbidity.\textsuperscript{26,44}

Conclusions

While results from COSS were disappointing to cerebrovascular neurosurgeons and vascular neurologists, a certain satisfaction should be derived from the rigorous scientific empiricism by which this important clinical question was investigated and, subsequently, answered. While COSS has unequivocally narrowed the indications for EC-IC bypass in the setting of ischemic cerebrovascular disease, it remains a challenge to the next generation of cerebrovascular neurosurgeons to develop and investigate novel surgical treatments for this disease process and to establish clinical benefit through well-conducted randomized controlled trials.

Disclosure

Dr. Derdeyn is a consultant for W. L. Gore and Associates (scientific advisory board), Penumbra Inc. (Data and Safety Monitoring Board for clinical trial), Silk Road (Chair, Data and Safety Monitoring Board for clinical trial), Microvention (Angio Core Lab LVIS Trial), and Equity: Pulse Therapeutics (Chair, Scientific Advisory Board; stock options). Dr. Grubb Jr. is a consultant for Edge Therapeutics, Inc. (member DSMB for drug safety trial).

Author contributions to the study and manuscript preparation include the following, Conception and design: all authors. Acquisition of data: Reynolds. Analysis and interpretation of data: all authors. Drafting the article: Zipfel, Reynolds, Grubb, Powers. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Zipfel. Administrative/technical/material support: Zipfel. Study supervision: Zipfel.

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