# Extracranial-Intracranial Bypass Surgery for Stroke Prevention in Hemodynamic Cerebral Ischemia
## The Carotid Occlusion Surgery Study Randomized Trial

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ATHEROSCLEROTIC INTERNAL carotid artery occlusion (AICAO) causes approximately 10% of transient ischemic attacks (TIAs) and 15% to 25% of ischemic strokes in the carotid territory.[1,2] The 2-year risk of subsequent ipsilateral ischemic stroke while a patient receives medical therapy is 10% to 15%.[1-3] Extracranial-intracranial (EC-IC) arterial bypass surgery was developed to prevent subsequent stroke by improving hemodynamics distal to the occluded artery.[4] In 1985, a randomized trial demonstrated no benefit of this surgery in 808 patients with symptomatic carotid artery occlusion.[5] This trial was criticized for failing to identify the subgroup of patients with hemodynamic cerebral ischemia due to poor collateral circulation for whom surgical revascularization might be of greatest benefit.[6-8]

Subsequent advances in neuroimaging have made it possible to identify those with hemodynamic cerebral ischemia who are at high risk for subsequent stroke when treated medically.[3,9-11] We conducted the Carotid Occlusion Surgery Study (COSS) to determine whether EC-IC bypass surgery, added to best medical therapy, reduces subsequent ipsilateral ischemic stroke at 2 years in patients with recently symptomatic AICAO and hemo-

**Context** Patients with symptomatic atherosclerotic internal carotid artery occlusion (AICAO) and hemodynamic cerebral ischemia are at high risk for subsequent stroke when treated medically.

**Objective** To test the hypothesis that extracranial-intracranial (EC-IC) bypass surgery, added to best medical therapy, reduces subsequent ipsilateral ischemic stroke in patients with recently symptomatic AICAO and hemodynamic cerebral ischemia.

**Design** Parallel-group, randomized, open-label, blinded-adjudication clinical treatment trial conducted from 2002 to 2010.

**Setting** Forty-nine clinical centers and 18 positron emission tomography (PET) centers in the United States and Canada. The majority were academic medical centers.

**Participants** Patients with arteriographically confirmed AICAO causing hemispheric symptoms within 120 days and hemodynamic cerebral ischemia identified by ipsilateral increased oxygen extraction fraction measured by PET. Of 195 patients who were randomized, 97 were randomized to receive surgery and 98 to no surgery. Follow-up for the primary end point until occurrence, 2 years, or termination of trial was 99% complete. No participant withdrew because of adverse events.

**Interventions** Anastomosis of superficial temporal artery branch to a middle cerebral artery cortical branch for the surgical group. Antithrombotic therapy and risk factor intervention were recommended for all participants.

**Main Outcome Measure** For all participants who were assigned to surgery and received surgery, the combination of (1) all stroke and death from surgery through 30 days after surgery and (2) ipsilateral ischemic stroke within 2 years of randomization. For the nonsurgical group and participants assigned to surgery who did not receive surgery, the combination of (1) all stroke and death from randomization to randomization plus 30 days and (2) ipsilateral ischemic stroke within 2 years of randomization.

**Results** The trial was terminated early for futility. Two-year rates for the primary end point were 21.0% (95% CI, 12.8% to 29.2%; 20 events) for the surgical group and 22.7% (95% CI, 13.9% to 31.6%; 20 events) for the nonsurgical group ($P=.78$, $Z$ test), a difference of 1.7% (95% CI, −10.4% to 13.8%). Thirty-day rates for ipsilateral ischemic stroke were 14.4% (14/97) in the surgical group and 2.0% (2/98) in the nonsurgical group, a difference of 12.4% (95% CI, 4.9% to 19.9%).

**Conclusion** Among participants with recently symptomatic AICAO and hemodynamic cerebral ischemia, EC-IC bypass surgery plus medical therapy compared with medical therapy alone did not reduce the risk of recurrent ipsilateral ischemic stroke at 2 years.

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dynamic cerebral ischemia identified by positron emission tomography (PET) measurements of oxygen extraction fraction (OEF).

## METHODS

The COSS was a parallel-group, 1:1 randomized, open-label, blinded-adjudication treatment trial conducted at 49 clinical centers and 18 PET centers in the United States and Canada. Personnel at the clinical coordinating center, including the principal investigator and project manager, were blinded to treatment assignment and to outcome, but persons who paid local sites or processed postoperative PET scans knew treatment assignment. Protocol amendments were made during the trial with approval of the data and safety monitoring board (DSMB) appointed by the National Institute of Neurological Disorders and Stroke (eMethods 1, available at http://www.jama.com). This description is based on the final protocol (copy available on request).

Potential participants were identified by monitoring vascular imaging studies and soliciting referrals from physicians. Primary clinical inclusion criteria were (1) vascular imaging demonstrating complete occlusion of an internal carotid artery and (2) TIA or ischemic stroke in the hemispheric territory of an occluded internal carotid artery in the preceding 120 days. (eMethods 2 has a full list of clinical eligibility criteria.) Participants who fulfilled initial clinical eligibility criteria provided written informed consent according to local institutional review board regulations and proceeded to PET.

Participants underwent PET at COSS-approved PET sites (US Food and Drug Administration Investigational New Drug Application 62,657). Forty-second emission images were compiled from 2-second dynamic images obtained following intravenous administration of 75 mCi $H_2^{15}O$ and following inhalation of 100 mCi $O^{15}O$. Ipsilateral-to-contralateral ratios of mean regional carotid territory OEF were calculated at Washington University from a quotient image of $O^{15}O/H_2^{15}O$ PET counts.[11] A ratio greater than 1.130 was required. Intra-arterial catheter arteriography documenting occlusion of the symptomatic internal carotid artery and intracranial and extracranial arteries suitable for anastomosis was also required.

Baseline clinical evaluation was performed prior to PET. Data on race/ethnicity in fixed categories were collected according to National Institutes of Health clinical trial requirements, with self-reporting or self-identification the preferred method.

We generated 1:1 randomization sequences using permuted blocks with stratification for clinical site and to ensure comparable numbers with contralateral carotid stenosis in each group using the SAS uniform random number generator (RANUNI). Sequences for each clinical site were loaded into a secure part of the COSS SQL server database. When a local investigator received notification of PET eligibility and entered the information from the Initial Eligibility and Arteriography forms, treatment assignment was obtainable from the COSS Web site.

Surgical intervention was microsurgical end-to-side anastomosis of a superficial temporal artery branch to a cortical branch of the middle cerebral artery (**FIGURE 1**). If the superficial temporal branch was unsuitable, the occipital artery could be used. Neurosurgeons were certified by attendance at a 2-day training workshop with videotaped instruction and surgical practice of microvascular anastomosis or demonstration of 80% or greater graft patency and rates of 10% or lower for stroke and death at 1 month in at least 10 consecutive previous EC-IC bypass surgeries. Alternatively, some neurosurgeons with fewer than 10 previous cases received a provisional certification to perform EC-IC bypass on a participant enrolled in COSS under the supervision of the neurosurgical principal investigator or designate.

Both treatment groups were prohibited from undergoing any additional or subsequent surgical procedure that might alter cerebral hemodynamics or affect stroke risk, except carotid endarterectomy for development of symptomatic contralateral carotid stenosis. For participants in the surgical group, preoperative and postoperative antithrombotic treatment was determined by the COSS neurosurgeon until they were returned to the antithrombotic treatment preferred by their physicians. Participants in the nonsurgical group continued to receive the antithrombotic treatment preferred by their physicians. Target levels for risk factor control were 130/85 mm Hg for blood pressure, 100 mg/dL for low-density lipoprotein cholesterol, 150 mg/dL for triglycerides, and 7% for hemoglobin $A_{1c}$. (To convert low-density lipoprotein cholesterol to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113.)

### Follow-up and Outcome Measures

The first follow-up visit was 30 to 35 days after randomization. Surgical participants received a repeat PET scan 30 to 60 days postoperatively. Subsequent follow-up visits were at 3-month intervals until 24 months or the end of the trial. Each follow-up examination included the following: history and examination to identify new stroke performed by an investigator other than the operating neurosurgeon; recording of current medications by class; National Institutes of Health Stroke Scale (NIHSS), modified Barthel Index, modified Rankin Scale, and stroke-specific quality of life (SS-QOL) assessment[12-16]; monitoring of risk factors; and Doppler examination to assess graft patency for the surgical group. Telephone follow-up was permitted if an in-person visit was impossible.

The primary end point for all participants randomized to the surgical group who received surgery was the combination of (1) all stroke and death from surgery through 30 days after surgery and (2) ipsilateral ischemic stroke within 2 years of randomization. The primary end point in the nonsurgical group and for those randomized to the

surgical group who did not receive surgery was the combination of (1) all stroke and death from randomization to randomization plus 30 days and (2) ipsilateral ischemic stroke within 2 years of randomization. Thus, those randomized to surgery who never underwent surgery were still analyzed in the surgical group, but the 30-day period to count all stroke and death for the primary end point began at randomization, not at surgery. Ipsilateral ischemic stroke was defined as the clinical diagnosis of a focal neurological deficit due to cerebral ischemia clinically localizable within the territory of the symptomatic occluded internal carotid artery that lasted for more than 24 hours.

Secondary end points were the following: all stroke, disabling stroke, fatal stroke, death, NIHSS score, modified Barthel Index, modified Rankin Scale score, and SS-QOL score.[12-16] The combination of any stroke or death was added as a post hoc end point. All stroke was defined as the clinical diagnosis of a focal deficit due to ischemia or hemorrhage clinically localizable to the brain lasting more than 24 hours. Fatal stroke led directly to the participant's death within 30 days of occurrence. Disabling stroke was defined as a modified Barthel Index of less than 12 of 20 at the first scheduled return visit more than 3 months after the stroke occurred.

All participants and their families were urged to contact the local study coordinator for any event that might be a stroke or in the event of death. The local site sent copies of all brain im-

**Figure 1.** Extracranial-Intracranial Bypass Surgery for Revascularization of an Occluded Internal Carotid Artery
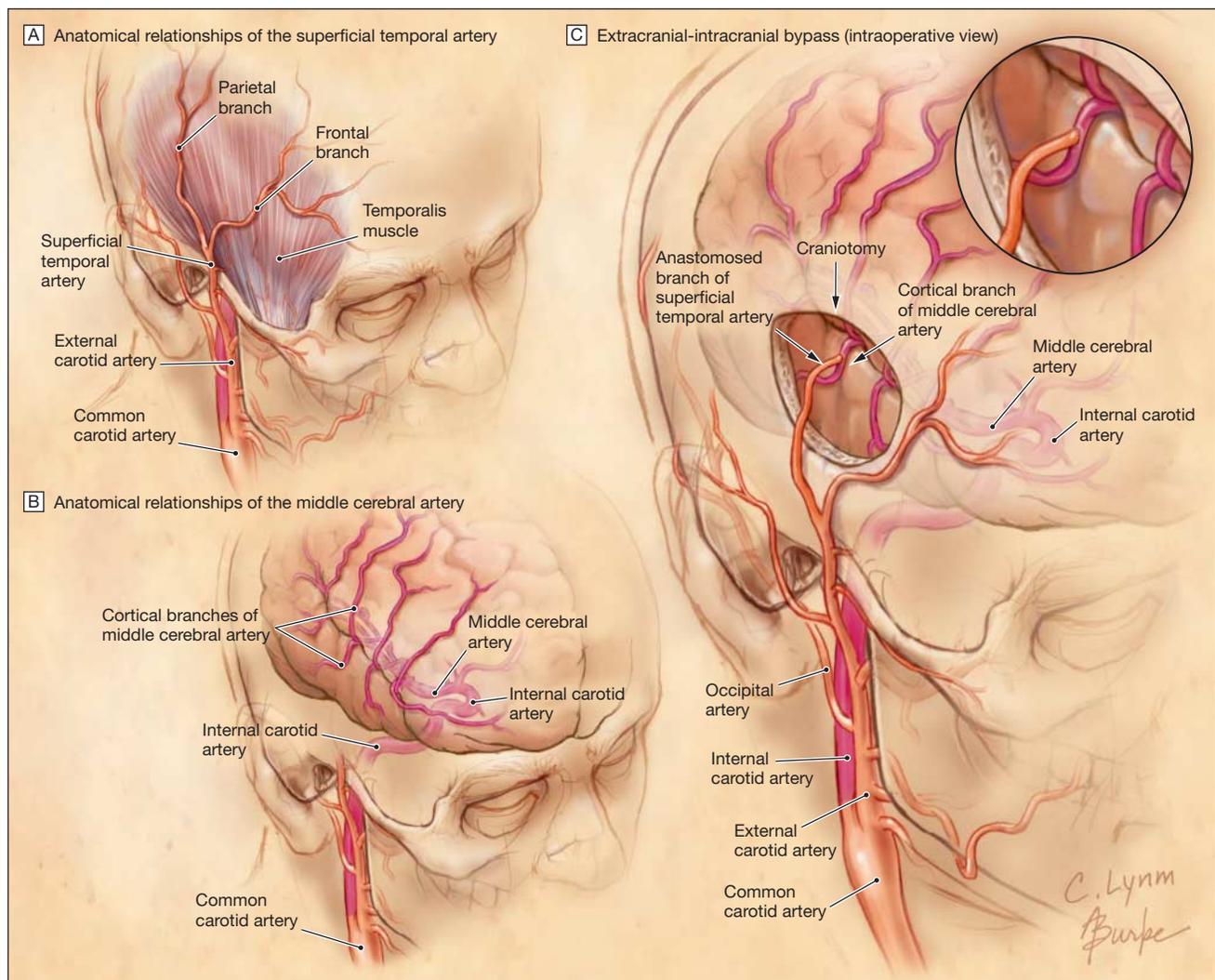


A and B, Anatomical relationships of the superficial temporal artery and middle cerebral artery. C, Intraoperative view showing completed anastomosis prior to closure of the dura, replacement of the bone flap, and closure of the soft tissues. The temporalis fascia, periosteum, subcutaneous fat, and dura are not depicted.

ages and arteriography obtained for clinical purposes and any other relevant information to the statistical data and management center within 1 week. A summary that contained no information to identify treatment group was prepared for 2 members of the adjudication committee. If they disagreed, the summary was sent to a third adjudicator. If the third adjudicator did not agree with either of the first 2, there was a consensus vote among all 3. All stroke end points determined by the adjudication committee were classified into stroke subtypes according to the TOAST criteria.[17]

A local safety monitor reviewed monthly summary reports of all adverse events by blinded treatment assignment. The National Institute of Neurological Disorders and Stroke appointed a DSMB that met at regular intervals.

## Sample Size Calculation and Data Analysis

Sample size and power calculations assumed that the true primary outcome rates would be 40% in the nonsurgical group and 24% in the surgical group. The eligibility criteria for COSS were selected based on our 1992-1997 prospective study of patients with symptomatic AICAO to match a high-risk subgroup with hemispheric symptoms within 120 days and a specific OEF threshold who had an overall rate of ipsilateral stroke at 2 years of 40% while receiving medical therapy.[3,18] Surgical morbidity and mortality were assumed to be 12% as in the EC-IC Bypass Trial and the 2-year postoperative ipsilateral stroke rate was assumed be 12%, as it was for persons with normal OEF in our previous study.[3,5] For a 5% 2-sided test to have 90% power to detect this difference, 354 participants (177 per group) were required (nQuery Advisor version 4, Statistical Solutions). To account for death from nonstroke causes, the sample size was increased by 5% to 372.

Baseline characteristics were compared using generalized Fisher exact tests for categorical variables and Wil-

coxon rank sum tests for continuous variables. For the primary end point, rates were based on product limit estimates of 2-year rates and their standard errors. Participants were censored at their last follow-up visit. We did not impute values for participants who were not followed up for the full 2 years. The test statistic was calculated as the difference in estimated rates divided by the standard error of that difference. The 2-sided $Z$ statistic was compared with a standard unit normal distribution. All randomized participants were analyzed in the treatment group to which they were initially randomized (intention-to-treat principle).

Secondary end points of any stroke, fatal stroke, disabling stroke, death and any stroke, or death were analyzed using the same methods. The Barthel Index was dichotomized as 19 to 20 vs less than or equal to 18, using a scale of 1 to 20. The modified Rankin Scale score was dichotomized in 2 ways: 0 or 1 vs 2 through 6 and 0 through 2 vs 3 through 6. These are standard dichotomizations used in stroke clinical trials.[19-21]

For dichotomized outcomes, differences between treatments were compared using Fisher exact tests. Summary SS-QOL scores were compared using a $t$ test. An on-treatment analysis was performed by removing participants assigned to the surgical group who never underwent surgery and censoring on the day of surgery participants assigned to the nonsurgical group who underwent EC-IC bypass surgery. SAS version 9.2 was used in the analyses.

The method of DeMets and Lan[22] with the O'Brien-Fleming type spending function was used for interim analyses for efficacy assuming 2-sided 5% level test. A futility analysis was performed at each interim analysis for efficacy. Thresholds for futility were computed in a manner similar to that used for interim stopping for efficacy with a newly developed method approved by the DSMB that controls the overall probability of a type II error at no more than 15% level, slightly more liberal than the 10% used for the primary efficacy outcome.[23] This method

allows the trial to stop early for futility with larger conditional power than more conventionally used and subjectively determined fixed thresholds of 10% to 15%.[23] Conditional power was computed for 3 alternatives: for the null hypothesis, for the currently observed rates, and for the original design effect size. The conditional power applied to prespecified futility thresholds was that based on the assumption of the original design effect size. Futility analyses included only those participants who had completed the 2-year follow-up to allow for the expected early perioperative stroke rate in the surgical group to be counterbalanced by longer-term reductions.

## Early Trial Termination

The second interim analysis was conducted when 194 participants had been randomized. The futility analysis included 139 participants who had completed 2-year follow-up: 16 primary end points in 74 surgical group patients and 11 primary end points in 65 nonsurgical group patients. Conditional power based on the assumption of the original design effect size was 29%, which crossed the prespecified futility boundary of 35%. The interim analysis for efficacy showed a between-group difference in favor of the nonsurgical group of 5.0% (95% CI, −12.5% to 11.5%).

The DSMB considered redesigning the trial to detect a smaller absolute difference of 10% in favor of surgery. This would have required increasing the overall sample size from 372 to 986 to achieve 80% power. The DSMB recommended stopping the trial, citing that (1) the prespecified statistical boundary for declaring futility had been crossed using the design effect size and, (2) given the unexpected relatively low rate of observed primary end points in the nonsurgical group, a clinically meaningful difference in favor of surgery would not be detectable without a substantial increase in sample size, which was not feasible. The study was terminated on June 24, 2010.

In December 2010, the DSMB was notified of errors in the interim analysis program. One patient in the non-

surgical group with a vertebrobasilar stroke occurring after 30 days had been erroneously included in the efficacy analysis. Three additional primary end points in the nonsurgical group had not been included in the futility analysis. These had been adjudicated as primary end points by the adjudication committee, but the computer program for the earlier analysis was not properly written with the correct event codes (2 were fatal strokes and 1 was an ipsilateral stroke occurring after a non–primary end point nonipsilateral stroke).

The conditional power recomputed based on the accurate data was 1% for the null hypothesis, 2% for the currently observed rates, and 50% for the original design effect size. The conditional power for the original design effect size did not cross the prespecified futility boundary of 35%. Nevertheless, the trial remained closed. The analyses presented here based on a closure date of June 24, 2010, include all 195 participants randomized by that date and all end points as of that date, including the 3 participants not included in the original futility analysis.

## RESULTS

Between June 2002 and June 2010, 195 participants were randomized: 97 to the surgical group and 98 to the nonsurgical group (**FIGURE 2**). Comparison of 24 baseline variables produced 1 difference at the $P < .05$ level in systolic blood pressure (**TABLE 1**). Follow-up for the primary end point until occurrence, 2 years, or termination of the trial was 99% complete (Figure 2). Median follow-up for the surgical group was 723 days (interquartile range [IQR], 288-730) and for the nonsurgical group was 722 days (IQR, 271-730). At last follow-up visit, risk factor control was similar in both groups (**TABLE 2**). Forty-three of the last available 3-month visits were by telephone, for which there were no measurements of risk factor control.

All primary end points were ipsilateral ischemic strokes, 20 in each group. In the surgical group, 19 were due to large artery atherosclerosis and 1 was

undetermined. In the nonsurgical group, 16 were due to large artery atherosclerosis, 3 were undetermined, and 1 was due to small artery occlusion (lacune). For the intention-to-treat analysis of the primary end point, the 2-year rates were 21.0% (95% CI, 12.8% to 29.2%) for the surgical group and 22.7% (95% CI, 13.9% to 31.6%) for the nonsurgical group ($P = .78$, $Z$ test), a difference of 1.7% (95% CI, −10.4% to 13.8%) (**TABLE 3** and **FIGURE 3**).

The confidence interval of the difference excludes the original design effect size of 16% in favor of surgery. Given the data at termination, and if the true 2-year rate in the surgical group is 21.0%, then the true rate in the nonsurgical group would need to be more than 30% for the conditional power to exceed 20%. This is at the extreme of

the 95% CI of 31.6% for the rates at termination. Similarly, given the data at termination and if the true 2-year rate in the nonsurgical group is 22.7%, the true rate in remaining patients in the surgical group would need to be less than 14% for the conditional power to exceed 20%. This is less than the perioperative rate of 15% observed at termination.

At 30 days, the rates of ipsilateral ischemic stroke were 14.4% (14/97) in the surgical group and 2.0% (2/98) in the nonsurgical group, a difference of 12.4% (95% CI, 4.9% to 19.9%). For the intention-to-treat analyses of the secondary end points, there were no significant differences at the .05 level (Table 3).

Four participants randomized to the surgical group did not undergo surgery (Figure 2). One had an ipsilateral ische-

**Figure 2.** Carotid Occlusion Surgery Study (COSS) Flow Diagram
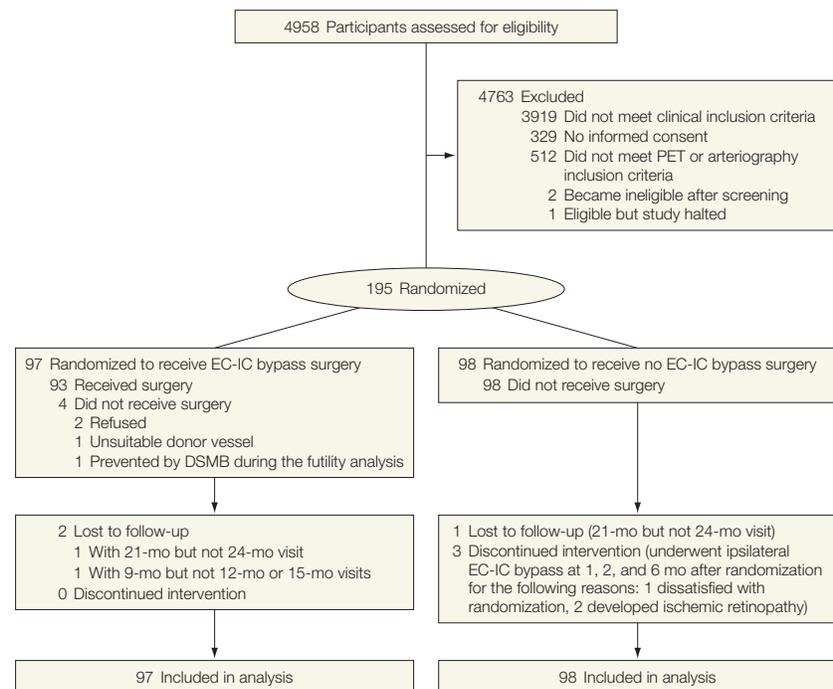


The 10 most common reasons recorded for failure of screened participants to meet clinical eligibility criteria were as follows: transient ischemic attack or stroke not in territory of occluded carotid artery (n=1597), transient ischemic attack or stroke not within preceding 120 days (n=485), language comprehension not intact (n=283), nonatherosclerotic condition causing carotid artery occlusion (n=280), modified Barthel Index not ≥12/20 (n=168), unsuitable surgical candidate (n=160), no occlusion of 1 internal carotid artery (n=114), not competent to give informed consent (n=110), subsequent surgery planned that might alter cerebral hemodynamics (n=105), age not 18-85 years (n=104). For each screened participant, only 1 reason needed to be provided. PET indicates positron emission tomography; EC-IC, extracranial-intracranial; DSMB, data and safety monitoring board.

mic stroke (primary end point) 9 months after randomization. Three participants randomized to the nonsurgical group underwent ipsilateral EC-IC bypass (Figure 2). One had an early postoperative ipsilateral ischemic stroke (primary end point). For the on-treatment analysis, the 2-year estimates for the pri-

**Table 1.** Baseline Characteristics[a]

| | Surgical Group (n = 97) | Nonsurgical Group (n = 98) | P Value[b] |
|---|---|---|---|
| Age, mean (SD), y | 58 (9) | 58 (9) | .71 |
| Male sex | 69 (71) | 61 (62) | .22 |
| White race | 88 (91) | 92 (94) | .65 |
| Hypertension | 76 (78) | 77 (79) | .99 |
| Atrial fibrillation | 1 (1) | 2 (2) | .99 |
| Hyperlipidemia | 79 (81) | 86 (88) | .45 |
| Diabetes mellitus | 21 (22) | 23 (23) | .93 |
| Cigarette smoking | | | |
|   Current | 33 (34) | 37 (38) | |
|   Former | 56 (58) | 51 (52) | .86 |
|   Never | 7 (7) | 9 (9) | |
|   Unknown | 1 (1) | 1 (1) | |
| Previous myocardial infarction | 11 (11) | 14 (14) | .83 |
| Previous stroke | 44 (45) | 35 (36) | .34 |
| Entry event type[c] | | | |
|   Stroke | 52 (54) | 62 (63) | |
|   Transient ischemic attack | 44 (45) | 35 (36) | .39 |
|   Unknown | 1 (1) | 1 (1) | |
| Entry event side | | | |
|   Right | 54 (56) | 45 (46) | .20 |
|   Left | 43 (44) | 53 (54) | |
| Entry event to randomization, mean (SD), d | 72 (37) | 75 (36) | .50 |
| PET ratio, mean (SD) | 1.26 (0.14) | 1.26 (0.14) | .76 |
| Contralateral carotid stenosis, % | | | |
|   <50 | 79 (81) | 78 (81) | |
|   50-69 | 11 (11) | 7 (7) | .41 |
|   ≥70 | 7 (7) | 11 (11) | |
|   Unknown | 0 | 2 (2) | |
| Assessment scores[d] | | | |
|   Modified Barthel Index, mean (SD) | 19.3 (1.8) | 19.5 (1.4) | .66 |
|   Modified Rankin Scale, mean (SD) | 1.4 (1.1) | 1.4 (1.1) | .63 |
|   NIHSS, median (IQR) | 1.0 (0-3) | 1.0 (0-3) | .31 |
|   SS-QOL summary, mean (SD) | 3.7 (0.9) | 3.7 (0.8) | .78 |
| Systolic blood pressure, mean (SD), mm Hg | 133 (15) | 139 (20) | .04 |
| Diastolic blood pressure, mean (SD), mm Hg | 76 (11) | 77 (10) | .36 |
| LDL cholesterol, mean (SD), mg/dL[e] | 107 (46) | 105 (36) | .85 |
| Triglycerides, mean (SD), mg/dL[e] | 186 (118) | 176 (167) | .17 |
| Hemoglobin $A_{1c}$, mean (SD), %[e] | 6.0 (1.0) | 6.1 (1.1) | .29 |

Abbreviations: IQR, interquartile range; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; PET, positron emission tomography; SS-QOL, stroke-specific quality of life.
SI conversion factors: To convert LDL cholesterol level to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.
[a] Values are number (percentage) unless otherwise indicated.
[b] P values were computed using Fisher exact tests for categorical variables and Wilcoxon rank sum statistics for continuous variables.
[c] Focal ischemic symptoms in the territory of the occluded carotid artery were categorized as cerebral transient ischemic attack (<24-h duration) or cerebral infarct (≥24-h duration).
[d] The modified Barthel Index (range, 0-20) evaluates the degree of independence in day-to-day self-care activities; a higher score is better (indicates greater independence). The modified Rankin Scale (0-6) is intended to define the degree of a participant's functional disability; a lower score is better (indicates less functional disability). The NIHSS (0-42) is a quantitative neurological examination developed to measure the degree of neurological deficit due to stroke; a lower score is better (indicates less neurological deficit). The summary SS-QOL (1-4) asks how self-reported overall quality of life compares with that before stroke; a higher score is better (indicates better quality of life).
[e] LDL cholesterol, triglycerides, and hemoglobin $A_{1c}$ values are from the 3-month follow-up visit.

mary end point were 20.8% (95% CI, 12.4% to 29.1%) for the surgical group and 22.3% (95% CI, 13.3% to 31.2%) for the nonsurgical group ($P$=.81), a difference of 1.5% (95% CI, −10.7% to 13.7%).

Other than crossovers, there were 3 surgical treatment protocol violations in the surgical group (1 ipsilateral common carotid stent, 2 asymptomatic carotid endarterectomies) and 1 in the nonsurgical group (contralateral asymptomatic carotid endarterectomy). One additional participant in the nonsurgical group underwent a contralateral carotid endarterectomy for symptomatic carotid stenosis as permitted by the protocol. Central arteriographic eligibility review of 191 studies (4 missing) revealed that 2 were not catheter arteriograms and 3 were not atherosclerotic occlusions.

Ninety-three participants in the surgical group underwent surgery a median of 6 days (IQR, 1-13) after randomization. No strokes occurred within this period. Within 30 days postoperatively, 14 of 93 patients (15%) experienced a stroke (all ipsilateral ischemic). Surgery was performed by 30 different surgeons. The surgical certification method was not significantly associated with 30-day postoperative stroke ($\chi^2$ Yates corrected, 0.196; $P$=.91). Serious adverse events occurred in 12 additional participants within the 30-day postoperative period: 4 TIAs, 2 epidural/subdural hematomas, 2 seizures, 1 myocardial infarction, 1 respiratory disorder, 1 hypotension, and 1 wound infection. In the nonsurgical group, the only serious adverse events within 30 days of randomization were 2 primary end point ipsilateral ischemic strokes.

Graft patency was 98% at 30 days (88/90 with data) and 96% at last follow-up (86/90). The mean OEF ratio in the surgical group improved from 1.258 at baseline to 1.109 at the 30- to 60-day postoperative repeat PET scan (87 patients with data).

## COMMENT

Despite excellent graft patency and improved cerebral hemodynamics in

the surgical group, EC-IC bypass surgery failed to provide an overall benefit on 2-year stroke recurrence. The 2-year primary end point rate of 21% in the surgical group was close to the rate of 24% projected from historical data. The 30-day postoperative morbidity and mortality of 15% was not statistically significantly different from the rate of 12% (81/663) from the EC-IC Bypass Trial ($P=.44$, $\chi^2$).[5] After the 30-day postoperative period, the rate of recurrent stroke for the remainder of the 2-year follow-up period was 6%, half of the 12% rate projected. In contrast, the 2-year primary end point rate of 23% in the nonsurgical group was much lower than the rate of 40% projected from a prospective observational study of similar patients carried out from 1992-1997.

The lower stroke risk observed in the COSS for the nonsurgical group is similar to the better outcomes observed in more recent studies of patients with medically treated asymptomatic carotid artery stenosis, ascribed to improvements in medical therapy.[24] These observations reaffirm the hazard of using even the most carefully studied

historical controls to infer therapeutic efficacy and the necessity of performing randomized controlled trials to establish clinical benefit. Although improved hemodynamics in participants who survived EC-IC bypass surgery without perioperative stroke was associated with low risk of recurrent stroke, the better-than-expected efficacy of medical therapy in the nonsurgical group was sufficient to nullify any overall benefit of surgery.

The COSS was terminated based on a futility analysis that showed a 29% chance of demonstrating a statistically significant benefit for surgery if taken to completion, under the assumption that the original design effect size was true. The value of 29% was below the prespecified threshold of 35%. It was later determined that there was an error in the analysis and that the conditional probability under the assumption of the original design effect size was 50%.

Computing conditional probability requires an assumption about the trends to be observed in the remainder of the study. Commonly used assumptions are the original design effect size (as used here for the threshold calculation) or the observed data.[25] Use of the origi-

**Table 2.** Medical Therapy and Risk Factor Status at Last Follow-up

| | No./Total No. (%) | | |
| --- | --- | --- | --- |
| | Surgical Group (n = 97) | Nonsurgical Group (n = 98) | P Value[a] |
| Use of antithrombotic medication | 89/95 (94) | 88/94 (94) | .99 |
| Systolic blood pressure ≤130 mm Hg | 34/76 (45) | 29/69 (42) | .87 |
| Diastolic blood pressure ≤85 mm Hg | 62/76 (82) | 48/69 (70) | .12 |
| Not currently smoking cigarettes | 60/95 (63) | 57/92 (62) | .79 |
| LDL cholesterol ≤100 mg/dL | 46/72 (64) | 44/62 (71) | .46 |
| Triglycerides ≤150 mg/dL | 45/75 (60) | 42/64 (66) | .60 |
| Hemoglobin $A_{1c}$ ≤7% | 65/74 (88) | 53/64 (83) | .47 |

Abbreviation: LDL, low-density lipoprotein.
SI conversion factors: To convert LDL cholesterol level to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.
[a] Fisher exact test.

**Table 3.** Study Outcomes by Intention-to-Treat Analyses[a]

| | Surgical Group (n = 97) | | Nonsurgical Group (n = 98) | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | No. of Events | Estimated Rate, % (95% CI) | No. of Events | Estimated Rate, % (95% CI) | Difference, % (95% CI) | P Value[b] |
| Primary end point[c] | 20 | 21.0 (12.8 to 29.2) | 20 | 22.7 (13.9 to 31.6) | 1.7 (−10.4 to 13.8) | .78 |
| Secondary end points | | | | | | |
| Any stroke | 22 | 23.4 (14.8 to 32.0) | 24 | 26.9 (17.6 to 36.2) | 3.5 (−9.2 to 16.1) | .59 |
| Fatal stroke | 1 | 1.0 (0 to 3.1) | 2 | 2.4 (0 to 5.6) | 1.3 (−2.5 to 5.2) | .50 |
| Disabling stroke | 5 | 5.9 (0.8 to 10.4) | 2 | 2.4 (0 to 5.6) | −3.2 (−9.0 to 2.6) | .27 |
| Death | 1 | 1.0 (0 to 3.1) | 5 | 5.1 (0.2 to 9.9) | 4.0 (−1.2 to 9.7) | .13 |
| Any stroke or death | 22 | 23.4 (14.8 to 32.0) | 26 | 29.9 (20.1 to 39.8) | 6.5 (−6.5 to 19.6) | .33 |
| Modified Rankin Scale score 0-1[d] | 48 | 49.5 (39.5 to 59.4) | 42 | 42.9 (33.1 to 52.7) | −6.6 (−20.6 to 7.3) | .41 |
| Modified Rankin Scale score 0-2[d] | 68 | 70.1 (61.0 to 79.2) | 73 | 74.5 (65.9 to 83.1) | 4.4 (−8.2 to 16.9) | .70 |
| Modified Barthel Index 19-20[d] | 68 | 70.1 (61.0 to 79.2) | 70 | 71.4 (62.5 to 80.4) | 1.3 (−11.4 to 14.1) | .85 |
| Summary SS-QOL score, mean[d] | | 3.82 (3.60 to 4.04) | | 3.58 (3.37 to 3.79) | −0.24 (−0.54 to 0.07) | .13 |

Abbreviation: SS-QOL, stroke-specific quality of life.
[a] All stroke end points are 2-year Kaplan-Meier estimates of the proportions (95% CIs) based on 195 randomized participants. Deaths were of any cause within 2 years of randomization for all 195 randomized participants. There was 1 death (fatal stroke) in the surgical group on the day of surgery (day 7 after randomization). There were 5 deaths in the nonsurgical group: 2 fatal strokes (days 67 and 657 after randomization) and 3 nonstroke deaths due to pneumonia (day 564), sudden death (day 597), and stage IV lymphoma (day 725).
[b] Fisher exact test.
[c] The primary end point for all participants who were assigned to surgery and received surgery was the combination of (1) all stroke and death from surgery through 30 days after surgery and (2) ipsilateral ischemic stroke within 2 years of randomization. The primary end point in the nonsurgical group and for those participants assigned to surgery who did not receive surgery was the combination of (1) all stroke and death from randomization to randomization plus 30 days and (2) ipsilateral ischemic stroke within 2 years of randomization. Ipsilateral ischemic stroke was defined as the clinical diagnosis of a focal neurological deficit due to cerebral ischemia clinically localizable within the territory of the symptomatic occluded internal carotid artery that lasted for more than 24 hours.
[d] Rankin and Barthel end points (proportions) and the SS-QOL have worst case imputed for deaths and missing values.

**Figure 3.** Kaplan-Meier Cumulative Curves for the Analysis of the Primary End Point



No. at risk

| | 0 | 90 | 180 | 270 | 360 | 450 | 540 | 630 | 720 |
|---|---|---|---|---|---|---|---|---|---|
| EC-IC bypass (surgical group) | 97 | 80 | 79 | 77 | 69 | 67 | 65 | 65 | 53 |
| No EC-IC bypass (nonsurgical group) | 98 | 87 | 81 | 74 | 69 | 65 | 62 | 57 | 51 |
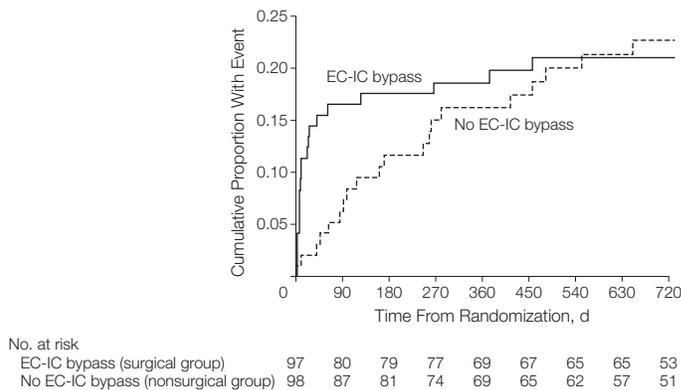
The primary end point is defined in the footnote to Table 3. The number of participants who remained event free and available for follow-up evaluation at each 90-day interval is shown. EC-IC indicates extracranial-intracranial.

nal design effect size assumes that the remainder of the participants enrolled in the trial will come from a population with the end point rates as originally postulated (in this case, 24% for the surgical group and 40% for the nonsurgical group). In the COSS, the assumption of the original design effect size was reasonable for the surgical group.

The perioperative stroke rate of 15% in the COSS was essentially identical to the rate of 12% from the EC-IC Bypass Trial. The post-perioperative stroke rate in the COSS surgical group was 6% in 2 years (3% per year) as compared with 4% per year for the 385 participants with carotid occlusion in the surgical group of the EC-IC Bypass Trial.[5] These data on the outcome of surgery are very consistent, and it is unlikely that additional participants enrolled in the surgical group of the COSS would have substantially different overall outcomes.

However, given the rate in the nonsurgical group of 22.7% with an upper 95% confidence bound of 31.6% observed at the time of the futility analysis, the assumption of the original design effect size of 40% for calculation of conditional power does not appear to be realistic. Using the alternative assumption based on the observed rates to calculate conditional power yields a probability of only 2% that the study would have rejected the null hypoth-

esis if all 372 originally scheduled participants had finished 2-year follow-up. Thus, it is highly unlikely that the COSS would have shown a statistically significant benefit for surgery if taken to completion.

Interpretation of the study is limited by the relatively small number of outcomes events. The 95% confidence bounds of the difference in the primary end point still allow for an absolute risk difference of 10% in favor of either group. Sham surgery was not performed, so there is the potential for bias in individual sites reporting potential end points for adjudication. This does not appear to have occurred, given that the number of reported events adjudicated not to be primary or secondary end points was 6 in the surgical group and 4 in the nonsurgical group.

The Japanese EC-IC Bypass Trial (JET) was similar in design to the COSS. The JET used the combination of reduced baseline cerebral blood flow and reduced cerebral blood flow increase in response to the vasodilator acetazolamide to identify patients with hemodynamic cerebral ischemia. From 1998-2002, 206 patients with major cerebral artery occlusive disease of the internal carotid artery or middle cerebral artery symptomatic within 3 months were enrolled. Final results of the 2-year follow-up were due in 2004. A second interim analysis of data from

196 patients followed up through January 2002 reported primary end points in 14 of 98 nonsurgically treated patients and 5 of 98 surgically treated patients ($P=.046$ by Kaplan-Meier analysis).[26,27] Examination of the published Kaplan-Meier curves show no end points within the first month in the surgical group. There is no explicit mention whether the results include 30-day postoperative morbidity and mortality, but it seems unlikely that this rate was 0 given that it was 12% in the original EC-IC Bypass Trial and 15% in the COSS. We are not aware of publication of the final JET results.

The COSS confirms the importance of hemodynamic factors in the pathogenesis of recurrent stroke in patients with symptomatic AICAO and the accuracy of PET measurements of OEF in identifying patients at high risk for recurrent stroke due to poor collateral circulation. The 23% rate of subsequent stroke at 2 years in these patients receiving medical therapy is comparable with that for patients with 70% to 99% symptomatic carotid stenosis.[28] Nevertheless, the results of the COSS showed that EC-IC bypass surgery provided no additional benefit over medical therapy for preventing recurrent stroke.

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