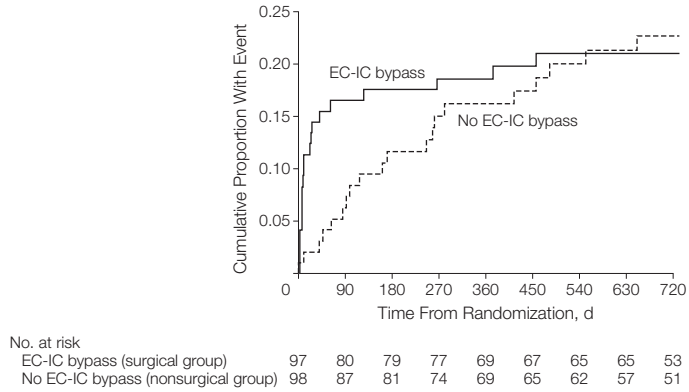
Figure 3. Kaplan-Meier Cumulative Curves for the Analysis of the Primary End Point



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 hypothesis 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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Author Contributions: Drs Powers and Clarke had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Study supervision: Powers, Clarke, Grubb.
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