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Extracranial-Intracranial Bypass and Risk of Stroke and Death in Patients With Symptomatic Artery Occlusion
The CMOSS Randomized Clinical Trial

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IMPORTANCE Prior trials of extracranial-intracranial (EC-IC) bypass surgery showed no benefit for stroke prevention in patients with atherosclerotic occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA), but there have been subsequent improvements in surgical techniques and patient selection.

OBJECTIVE To evaluate EC-IC bypass surgery in symptomatic patients with atherosclerotic occlusion of the ICA or MCA, using refined patient and operator selection.

DESIGN, SETTING, AND PARTICIPANTS This was a randomized, open-label, outcome assessor–blinded trial conducted at 13 centers in China. A total of 324 patients with ICA or MCA occlusion with transient ischemic attack or nondisabling ischemic stroke attributed to hemodynamic insufficiency based on computed tomography perfusion imaging were recruited between June 2013 and March 2018 (final follow-up: March 18, 2020).

INTERVENTIONS EC-IC bypass surgery plus medical therapy (surgical group; n = 161) or medical therapy alone (medical group; n = 163). Medical therapy included antiplatelet therapy and stroke risk factor control.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of stroke or death within 30 days or ipsilateral ischemic stroke beyond 30 days through 2 years after randomization. There were 9 secondary outcomes, including any stroke or death within 2 years and fatal stroke within 2 years.

RESULTS Among 330 patients who were enrolled, 324 patients were confirmed eligible (median age, 52.7 years; 257 men [79.3%]) and 309 (95.4%) completed the trial. For the surgical group vs medical group, no significant difference was found for the composite primary outcome (8.6% [13/151] vs 12.3% [19/155]; incidence difference, −3.6% [95% CI, −10.1% to 2.9%]; hazard ratio [HR], 0.71 [95% CI, 0.33-1.54]; $P = .39$). The 30-day risk of stroke or death was 6.2% (10/161) in the surgical group and 1.8% (3/163) in the medical group, and the risk of ipsilateral ischemic stroke beyond 30 days through 2 years was 2.0% (3/151) and 10.3% (16/155), respectively. Of the 9 prespecified secondary end points, none showed a significant difference including any stroke or death within 2 years (9.9% [15/152] vs 15.3% [24/157]; incidence difference, −5.4% [95% CI, −12.5% to 1.7%]; HR, 0.69 [95% CI, 0.34-1.39]; $P = .30$) and fatal stroke within 2 years (2.0% [3/150] vs 0% [0/153]; incidence difference, 1.9% [95% CI, −0.2% to 4.0%]; $P = .08$).

CONCLUSIONS AND RELEVANCE Among patients with symptomatic ICA or MCA occlusion and hemodynamic insufficiency, the addition of bypass surgery to medical therapy did not significantly change the risk of the composite outcome of stroke or death within 30 days or ipsilateral ischemic stroke beyond 30 days through 2 years.

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Visual Abstract

Editorial page 697

Supplemental content

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Intracranial atherosclerotic disease was a major contributor to ischemic stroke burden globally, accounting for approximately 10% of ischemic strokes in Western countries[1] and 50% in Asia in 2009.[2] Patients with symptomatic occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA) are subject to high annual recurrent stroke risks, exceeding 10% per year.[3-6] Furthermore, cerebral hemodynamic insufficiency identifies a subgroup of these patients with an even higher 2-year risk of ischemic stroke, despite medical therapy.[7]

Extracranial-intracranial (EC-IC) bypass surgery represents a plausible treatment strategy for patients with hemodynamically compromised ICA or MCA occlusion, aimed at restoring blood flow and reducing the risk of stroke by anastomosis of the superficial temporal artery to the MCA.[8] The EC/IC Bypass Study was the first randomized clinical trial demonstrating no benefit of bypass surgery in symptomatic patients with atherosclerotic stenosis or occlusion of the ICA and MCA.[9] This trial was criticized for including patients with atherosclerotic stenosis, who might be unlikely to benefit from bypass surgery, while also failing to identify patients with hemodynamic insufficiency, in whom bypass surgery might be of greatest benefit.[10] The Carotid Occlusion Surgery Study (COSS) in North America was halted early for futility, failing to demonstrate a benefit of bypass surgery in patients with hemodynamically compromised ICA occlusion.[11] Debates emerged as to whether reduction in perioperative risk could render bypass surgery effective, as the postoperative stroke rate was 15% in COSS.[12-14] Final results with adjudicated outcomes have not yet been published for a Japanese EC-IC bypass trial of 196 patients.[15]

After COSS was published in 2011, in the United States, the percentage of EC-IC bypasses performed for hospital-admitted patients with symptomatic artery occlusion decreased from 40% in 2008-2010 to 20% in 2011-2014.[16] In this context, the Carotid and Middle Cerebral Artery Occlusion Surgery Study (CMOSS) was designed as a multicenter, randomized, open-label trial comparing EC-IC bypass surgery plus medical therapy with medical therapy alone in symptomatic patients with ICA or MCA occlusion and hemodynamic insufficiency, with refined patient and operator selection.

Key Points

Question Among symptomatic patients with atherosclerotic occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA) with evidence of hemodynamic insufficiency in the affected territory, does extracranial-intracranial (EC-IC) bypass surgery plus medical therapy reduce stroke or death compared with medical therapy alone?

Findings In this randomized clinical trial that included 324 patients, the addition of bypass surgery to medical therapy did not significantly change the risk of the composite outcome of stroke or death within 30 days or ipsilateral ischemic stroke beyond 30 days through 2 years compared with medical therapy alone (8.6% vs 12.3%, respectively; hazard ratio, 0.71).

Meaning The findings do not support the addition of EC-IC bypass surgery to medical therapy for the treatment of patients with symptomatic atherosclerotic occlusion of the ICA or MCA.

Methods

Study Design and Oversight

CMOSS was a multicenter, randomized, open-label trial with blinded assessment of end points at 13 sites in China. Details of the study protocol have been previously published and are provided in Supplement 1.[17] A detailed statistical analysis plan is provided in Supplement 2. The trial was approved by ethics committees and research boards for each participating site and overseen by an independent data and safety monitoring board. Information on the trial design, leadership, committees, and investigators is provided in Supplement 3 and Supplement 4. All the patients or their legal representatives provided written informed consent.

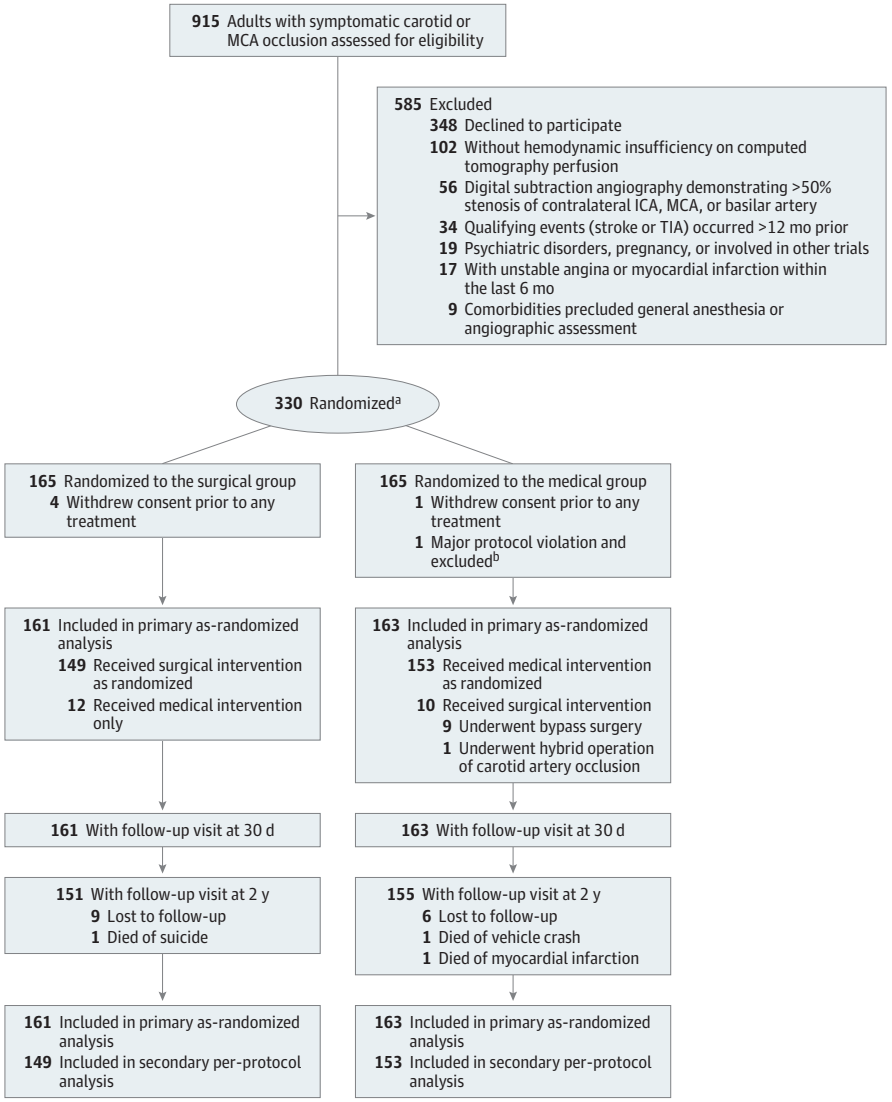
The first patient was enrolled on June 6, 2013, and the last patient on March 2, 2018. Each patient was followed up for 2 years after randomization. The 2-year follow-up for the last enrolled patient was completed on March 18, 2020.

Trial Population

Patients were eligible for inclusion in the trial if they were between 18 and 65 years, had an occlusion of a unilateral ICA or MCA demonstrated by digital subtraction angiography, and had a modified Rankin Scale (mRS) score of 0 to 2 (**Figure 1**; **Table 1**). A qualifying transient ischemic attack (TIA) or ischemic stroke in the territory of the occluded ICA or MCA must have occurred within the past 12 months, the most recent stroke must have occurred more than 3 weeks previously, and the neurologic deficit must have been stable for more than 1 month. Additionally, hemodynamic insufficiency within the MCA territory was required on imaging, defined as mean transit time (MTT) (symptomatic side) of longer than 4 seconds and relative cerebral blood flow (rCBF) (symptomatic side/asymptomatic side) of less than 0.95 on computed tomography perfusion. Detailed methods of quantitative measurement of MTT and CBF and the definition of region of interest were previously described.[18,19] Patients with more than 50% degree of stenosis of any other vessels (especially the contralateral ICA, contralateral MCA, or basilar artery) demonstrated by digital subtraction angiography, massive cerebral infarction (more than 50% of the MCA territory) demonstrated by computed tomography or magnetic resonance imaging, or other neurovascular disease likely to cause focal cerebral ischemia were excluded. Detailed eligibility criteria are provided in the eMethods in Supplement 3. An independent imaging core laboratory confirmed the imaging findings related to eligibility criteria.

Thirteen sites from 15 candidate academic tertiary centers in China met the following inclusion criteria: (1) attending neurosurgeons were certified by their roles as chief surgeon in at least 15 consecutive previous EC-IC bypass surgeries during the previous year and (2) an anastomosis patency rate greater than 95% and a perioperative stroke or death rate less than 10% according to the records from the prior year.

Figure 1. Patient Enrollment and Follow-Up in the Carotid and Middle Cerebral Artery Occlusion Surgery Study (CMOSS) Trial



ICA indicates internal carotid artery; MCA, middle cerebral artery; and TIA, transient ischemic attack.

[a] Simple randomization without block or stratification.

[b] Major protocol violation due to baseline modified Rankin Scale score of 4.

Randomization and Interventions

Patients were randomly assigned to EC-IC bypass surgery plus medical therapy (the surgical group) or medical therapy alone (the medical group) in a 1:1 ratio without block or stratification. Computer-generated random number by an interactive voice response system (Clinical Soft) was used for treatment assignment. After randomization, follow-up visits at the neurologic outpatient clinic were scheduled at 30 days as well as 6, 12, and 24 months.

All enrolled patients received optimized medical treatment including management of vascular risk factors. Risk factor management included low-density lipoprotein cholesterol level and hypertension control with medications as needed, as well as encouraging smoking cessation (eg, counseling or oral smoking cessation medications) and excess weight control (eg, behavioral change or medications), based on 2011 American Heart Association/American Stroke Association guidelines before 2014 and 2014 American Heart Association/American Stroke Association guidelines after 2014.[20,21] Aspirin (100 mg/day) or clopidogrel (75 mg/day) was prescribed to the patient and the use of any other antithrombotic therapy (specifically, oral anticoagulant agents) was discontinued until the 30-day follow-up visit.

Surgical intervention was performed within 7 days of randomization by certified surgeons. Standard end-to-side anastomosis of the superficial temporal artery to the M4 segment (MCA) was used. Major targets of perioperative management included the duration of the MCA cortical branch occlusion less than 30 minutes and steady intraprocedural arterial P_{CO_2} and periprocedural blood pressure. Specifically, continuous end-tidal P_{CO_2} needed to be calibrated with arterial blood P_{CO_2}, and if preoperative data were not available, noninvasive systolic blood pressure targets were between 130 and 150 mm Hg and P_{CO_2} targets were between 35 and 40 mm Hg.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline

Characteristic	No. (%)[a]	
	Surgical group (n = 161)	Medical group (n = 163)
Age, median (IQR), y	52.0 (43.9-58.4)	53.5 (46.7-59.1)
Sex		
Male	125 (77.6)	132 (81.0)
Female	36 (22.4)	31 (29.0)
Body mass index, median (IQR)[b]	24.5 (23.2-26.7)	25.2 (23.0-26.8)
Medical history		
Hypertension	97 (60.2)	93 (57.1)
Diabetes	35 (21.7)	33 (20.2)
Hyperlipidemia	15 (9.3)	22 (13.5)
Previous myocardial infarction	1 (0.6)	1 (0.6)
Atrial fibrillation	1 (0.6)	0
Peripheral artery disease	1 (0.6)	0
Received medication prior to latest qualifying event		
Antiplatelet therapy	134 (83.2)	145 (89.0)
Lipid-lowering therapy	38 (23.6)	61 (37.4)
Anticoagulant therapy	3 (1.9)	1 (0.6)
Smoking history		
Current	45 (28.0)	53 (32.5)
Former	38 (23.6)	34 (20.9)
Alcohol history		
Current	35/157 (22.3)	32/162 (19.8)
Former	29/157 (18.5)	24/162 (14.8)
Qualifying event		
Stroke	90 (55.9)	90 (55.2)
TIA	71 (44.1)	73 (44.8)
Latest ischemic event to randomization, median (IQR), d		
Stroke	65.5 (46.0-102.0)	73.0 (43.0-119.0)
TIA	58.0 (36.0-122.0)	54.0 (33.0-92.0)
Qualifying artery		
Carotid artery	87 (54.0)	99 (60.7)
Middle cerebral artery	74 (46.0)	64 (39.3)
Qualifying side		
Left	87 (54.0)	88 (54.0)
Right	74 (46.0)	75 (46.0)
Contralateral artery stenosis <50%		
Carotid artery	8 (5.0)	11 (6.7)
Middle cerebral artery	1 (0.6)	3 (1.8)
Computed tomography perfusion		
Mean transit time (qualifying side), median (IQR), s[c]	6.3 (5.1-9.0) [n = 153]	5.8 (4.9-7.6) [n = 157]
Relative cerebral blood flow (qualifying/contralateral side), median (IQR)[d]	0.8 (0.7-0.9) [n = 156]	0.7 (0.6-0.8) [n = 161]
NIHSS score, median (IQR)[e]	0.0 (0.0-2.0)	0.0 (0.0-2.0)
0	81 (50.3)	93 (57.1)
≥1	80 (49.7)	70 (42.9)
mRS score, median (IQR)[f]	1.0 (1.0-1.0)	1.0 (0.0-1.0)
0	36 (22.4)	46 (28.2)
1	89 (55.3)	85 (52.2)
2	36 (22.4)	32 (19.6)
Blood pressure, median (IQR), mm Hg		
Systolic	130.0 (121.0-140.0)	130.0 (120.0-140.0)
Diastolic	80.0 (75.0-87.0)	80.0 (73.0-85.0)

(continued)

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (continued)

Characteristic	No. (%)[a]	
	Surgical group (n = 161)	Medical group (n = 163)
Hemoglobin A_{1C}, median (IQR), %	5.8 (5.4-6.7) [n = 80]	5.8 (5.4-6.8) [n = 88]
LDL cholesterol level, median (IQR), mmol/L	1.9 (1.4-2.3) [n = 154]	2.0 (1.6-2.4) [n = 157]
Triglycerides level, median (IQR), mmol/L	1.3 (1.0-1.8) [n = 154]	1.5 (1.1-1.8) [n = 157]

Abbreviations: LDL, low-density lipoprotein; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

SI conversion factors: To convert LDL cholesterol to mg/dL, divide by 0.0259; triglycerides to mg/dL, divide by 0.0113.

[a] Data are reported as No. (%) unless otherwise indicated.

[b] Body mass index is the weight in kilograms divided by height in meters squared.

[c] Mean transit time designates the mean time required for a contrast bolus to traverse the voxel and is measured in seconds. Mean transit time is inversely proportional to cerebral perfusion pressure and prolonged value indicates arterial stenosis or occlusion.

[d] Cerebral blood flow refers to the volume of blood flowing in a unit of brain mass during a unit of time (measured in mL/100 g/min). Relative cerebral blood flow denotes symptomatic side/asymptomatic side.

[e] Scores on the NIHSS range from 0 to 42, with higher scores indicating a more severe neurologic deficit.

[f] Scores on the mRS range from 0 (no functional limitations) to 6 (death), with higher scores indicating more severe functional disability. A score of 2 or less indicates functional independence.

Outcome Measures and Definitions

The primary outcome was a composite of any stroke or death within 30 days after randomization or ipsilateral ischemic stroke beyond 30 days through 2 years after randomization. Secondary outcomes included (1) any stroke within 2 years; (2) disabling stroke within 2 years; (3) fatal stroke within 2 years; (4) death within 2 years; (5) any stroke or death within 2 years; (6) TIA within 2 years; (7) National Institutes of Health Stroke Scale (NIHSS) score and modified Rankin Scale (mRS) score within 2 years; (8) complications associated with the surgical procedures; and (9) anastomosis patency at 2 years.

A stroke was defined as rapidly developed clinical signs of focal or global disturbance of cerebral function that lasted more than 24 hours due to cerebral ischemia or hemorrhage, according to World Health Organization criteria. Ipsilateral ischemic stroke was further defined as the clinical diagnosis of a focal or global disturbance of cerebral function due to cerebral ischemia that was clinically localizable within the territory of the symptomatic occluded ICA or MCA and that lasted for more than 24 hours. Brain computed tomography or magnetic resonance image scanning was used to identify stroke. The mRS is a standard global 7-level measure of disability, ranging from 0 (no functional limitations) to 6 (death), with higher scores indicating more severe functional disability. Scores on the NIHSS range from 0 to 42, with higher scores indicating a more severe neurologic deficit. Disabling stroke was defined by any of the following: (1) an mRS score of 3 or more; (2) an increase of at least 1 point in the mRS score from prestroke baseline; (3) a score on the composite NIHSS of 7 or more; or (4) an increase of at least 4 points in the NIHSS score from prestroke baseline. Detailed definitions are provided in Supplement 1. An independent outcome committee and imaging core laboratory determined the primary and secondary outcomes, blinded to treatment assignment.

Sample Size Calculation

We assumed that the true primary outcome rates would be 28% in the medical group,[22-24] and there would be a 50% relative risk reduction in the surgical group. This meant that the primary outcome rate was assumed to be 14% in the surgical group. We estimated that 330 patients (165 per group) would provide 80% power using a 2-tailed α of 5% to detect an absolute 14% difference in the rate of primary outcome events in the surgical group (estimated as 14%) from that in the medical group (estimated as 28%), with an attrition rate of 20% during 2 years of follow-up.

Statistical Analysis

Outcome evaluation was conducted in both the full analysis set and per-protocol set, with analysis in the full analysis set as the primary analysis. The full analysis set population included all the patients who underwent randomization and treatment, and patients were analyzed according to their randomized groups. The difference in the primary outcome between groups was tested using log-rank test, with the center information (site effect) as a stratification factor. The same test was used to compare the secondary outcomes including 2-year any stroke, disabling stroke, fatal stroke, death, any stroke or death, and TIA between 2 groups. Kaplan-Meier curves were used to show the risk of time-to-event outcomes over time. Participants who were lost to follow-up or who died from nonstroke causes were censored at the time of occurrence. For other secondary outcomes and baseline characteristics, χ^2 or Fisher exact tests were used for categorical variables, and *t* or Wilcoxon rank tests for quantitative variables.

We estimated hazard ratios (HRs) with Cox proportional-hazards models for time-to-event analyses of the primary outcome and secondary outcomes. However, we also performed post hoc relative risk (RR) analyses for both primary and secondary outcomes as the underlying assumption of proportional hazards was not met with supremum test ($P < .001$). Participants lost to follow-up were presumed to not have experienced the event of interest for primary outcome and secondary outcomes in the RRs calculation. Other post hoc analyses included (1) analysis of the individual components of the primary outcome (ie, stroke or death within 30 days after randomization, ipsilateral ischemic stroke beyond 30 days through 2 years after randomization);

(2) subgroup analyses by age, sex, received medication prior to latest qualifying event (antiplatelet therapy, lipid-lowering therapy), qualifying event, time interval between the latest ischemic event to randomization (≤6 weeks, >6 weeks), qualifying artery, MTT (≤6 seconds, >6 seconds), and rCBF (≤0.8, >0.8). The interaction effects between interventions and the factors mentioned above were evaluated using the generalized linear regression model with the binomial distribution and log link function in the RRs subgroup analyses. The trial was not powered for and had no prespecified correction for multiple comparisons for a definitive analysis of secondary end points or subgroups. The findings for these analyses should be interpreted as exploratory.

All statistical tests were performed by 2-sided tests. A *P* value of .05 was considered to demonstrate a statistically significant difference. All analyses were performed with SAS software version 9.4 (SAS Institute).

Results

Between June 6, 2013, and March 2, 2018, a total of 915 patients with symptomatic ICA or MCA occlusion were screened at 13 sites; 330 patients were enrolled, with 165 each randomly assigned to the surgical and medical groups (eFigure 1 in Supplement 3). A total of 6 patients (4 in the surgical group and 2 in the medical group) immediately withdrew from the study without any treatment or data collection and were excluded from the full analysis set for final analysis. The remaining 324 patients (161 in the surgical and 163 in the medical group) were included in the full analysis set for final analysis. A total of 15 patients (4.6%) had incomplete follow-up for the primary outcome (Figure 1). The progress of the trial, such as on-site clarification and confirmation for data inquiries, was significantly delayed due to the COVID-19 pandemic.

Baseline characteristics were generally balanced between the 2 groups, except for the percentage of patients with previous lipid-lowering therapy and the level of triglycerides, which were lower in the surgical group, and the MTT of the qualifying side and rCBF, which were higher in the surgical group. The median age of the participants was 52.7 years (IQR, 44.6-58.7), and 257 (79.3%) were male. Among all 324 patients, 180 patients (55.6%) presented with index stroke as the qualifying event, and 186 (57.4%) were diagnosed as having ICA occlusion vs 138 (42.6%) as having MCA occlusion as the qualifying artery (Table 1). At the last follow-up visit, risk factor control was similar in both groups (eTable 1 in Supplement 3).

Primary Outcome

For the surgical group vs medical group, no significant difference was found for the primary outcome of risk of stroke or death (8.6% [13/151] vs 12.3% [19/155]; incidence difference, −3.6% [95% CI, −10.1% to 2.9%]; HR, 0.71 [95% CI, 0.33-1.54]; *P* = .39) (**Table 2** and **Figure 2**). The primary outcome was missing for 18 patients (10 in the surgical group and 8 in the medical group). Among patients assigned to the medical group, 10 patients crossed over to surgical procedures. Four patients were further lost to follow-up, 1 died of a vehicle crash, and 1 died of myocardial infarction beyond 30 days. Among patients assigned to the surgical group, 12 patients crossed over to medical treatment only. Nine patients were further lost to follow-up and 1 died of suicide beyond 30 days. The per-protocol analysis yielded similar results (9.4% [13/139] vs 10.9% [16/147]; incidence difference, −1.7% [95% CI, −8.4% to 4.9%]; HR, 1.09 [95% CI, 0.50-2.37]; *P* = .85) (eTable 2 in Supplement 3).

Secondary Outcomes

All secondary outcomes showed no significant difference between groups (Table 2; eFigures 2-8 in Supplement 3). The 2-year risk of any stroke or death was 9.9% (15/152) in the surgical group vs 15.3% (24/157) in the medical group (incidence difference, −5.4% [95% CI, −12.5% to 1.7%]; HR, 0.69 [95% CI, 0.34-1.39]; *P* = .30). The risk of fatal stroke within 2 years was 2.0% (3/150) in the surgical group vs 0% (0/153) in the medical group (incidence difference, 1.9% [95% CI, −0.2% to 4.0%]; *P* = .08). The risk of disabling stroke within 2 years was 4.1% (6/147) in the surgical group and 2.0% (3/153) in the medical group (incidence difference, 1.9% [95% CI, −1.7% to 5.5%]; HR, 1.75 [95% CI, 0.41-7.51]; *P* = .43). The 2-year mortality risk was 2.7% (4/151) in the surgical group vs 1.3% (2/155) in the medical group (incidence difference, 1.3% [95% CI, −1.7% to 4.2%]; HR, 3.72 [95% CI, 0.68-20.38]; *P* = .12). Anastomosis patency at 2 years in the surgical group was 93.6% (103/110). Other secondary outcomes are shown in Table 2.

Post Hoc Outcomes and Analyses

Post hoc analysis of the individual components of the primary outcome showed the 30-day risk of stroke or death was 6.2% (10/161) in the surgical group vs 1.8% (3/163) in the medical group, and the risk of ipsilateral ischemic stroke beyond 30 days through 2 years was 2.0% (3/151) in the surgical group vs 10.3% (16/155) in the medical group (Table 2; eFigures 9-10 in Supplement 3). In patients with MTT longer than 6 seconds, the primary outcome occurred in 7 (9.2%) of 76 patients in the surgical group and 12 (17.4%) of 69 patients in the medical group (incidence difference, −8.2% [95% CI, −18.7% to 2.3%]; HR, 0.57 [95% CI, 0.21-1.59]) (**Figure 3**). In patients with rCBF of 0.8 or less, the primary outcome occurred in 5 (6.4%) of 78 patients in the surgical group and 15 (14.0%) of 107 patients in the medical group (incidence difference, −7.4% [95% CI, −15.5% to 0.7%]; HR, 0.38 [95% CI, 0.13-1.18]) (Figure 3; eFigure 11 and eTable 3 in Supplement 3). Details of perioperative management in the surgical group are shown in eTable 4 in Supplement 3.

Discussion

This randomized clinical trial showed that, among patients with TIA or nondisabling ischemic stroke due to ICA or MCA occlusion and hemodynamic insufficiency, the primary outcome (a composite of stroke or death within 30 days or ipsilateral ischemic stroke beyond 30 days through 2 years)

Table 2. Primary and Secondary Outcomes

Outcome	No. (%)		Hazard ratio (95% CI)[a]	Incidence difference, % (95% CI)[b]	Relative risk (95% CI)[c]	*P* value[d]
	Surgical group (n = 161)	Medical group (n = 163)				
Primary outcome						
Stroke or death within 30 d or ischemic stroke in territory of qualifying artery beyond 30 d through 2 y	13/151 (8.6)	19/155 (12.3)	0.71 (0.33 to 1.54)	−3.6 (−10.1 to 2.9)	0.69 (0.35 to 1.36)	.39
Components of the primary outcome[e]						
Stroke or death within 30 d[f]	10/161 (6.2)	3/163 (1.8)				
Ischemic stroke in territory of qualifying artery beyond 30 d through 2 y	3/151 (2.0)	16/155 (10.3)				
Secondary outcomes						
Any stroke or death within 2 y	15/152 (9.9)	24/157 (15.3)	0.69 (0.34 to 1.39)	−5.4 (−12.5 to 1.7)	0.63 (0.34 to 1.16)	.30
Any stroke within 2 y	14/151 (9.3)	22/155 (14.2)	0.67 (0.33 to 1.39)	−4.8 (−11.6 to 2.0)	0.64 (0.34 to 1.21)	.29
Disabling stroke within 2 y[g]	6/147 (4.1)	3/153 (2.0)	1.75 (0.41 to 7.51)	1.9 (−1.7 to 5.5)	2.02 (0.52 to 7.96)	.43
Deaths within 2 y	4/151 (2.7)	2/155 (1.3)	3.72 (0.68 to 20.38)	1.3 (−1.7 to 4.2)	2.02 (0.38 to 10.91)	.12
TIA within 2 y	3/147 (2.0)	6/154 (3.9)	0.31 (0.08 to 1.30)	−1.8 (−5.4 to 1.8)	0.51 (0.13 to 1.99)	.10
Fatal stroke within 2 y	3/150 (2.0)	0/153	NA	1.9 (−0.2 to 4.0)	NA	.08
NHISS score at 2 y, median (IQR)[h]	0.0 (0.0 to 1.0) [n = 139]	0.0 (0.0 to 0.0) [n = 148]				.44[i]
0	101/139 (72.7)	113/148 (76.4)				.47[j]
≥1	38/139 (27.3)	35/148 (23.6)				
mRS score at 2 y, median (IQR)[k]	0.0 (0.0 to 1.0) [n = 148]	0.0 (0.0 to 1.0) [n = 151]				.51[i]
0	88/148 (59.5)	84/151 (55.6)				.51[i]
1	42/148 (28.4)	44/151 (29.1)				
2	8/148 (5.4)	18/151 (11.9)				
3	2/148 (1.4)	3/151 (2.0)				
4	4/148 (2.7)	0/151				
5	0/148	0/151				
6	4/148 (2.7)	2/151 (1.3)				
Complications associated with the surgical procedures[l]	6/149 (4.0)	NA				NA
Anastomosis patency at 2 y	103/110 (93.6)	NA				NA

Abbreviations: mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

[a] Cox proportional hazard model adjusted for site effect.

[b] Absolute incidence difference without adjustment.

[c] Post hoc analysis of relative risk adjusted for site effect based on the assumption that patients with missing data did not have the primary or secondary outcomes.

[d] Log-rank test adjusted for site effect.

[e] Individual elements of the primary outcome were analyzed post hoc.

[f] The mortality rate was 1.9% (3/161) in the surgical group and 0% (0/163) in the medical group. The stroke rate was 6.2% (10/161) and 1.8% (3/163), respectively.

[g] The rate of disabling stroke within 30 days was 1.9% (3/158) in the surgical group and 0% (0/163) in the medical group.

[h] Scores on the NIHSS range from 0 to 42, with higher scores indicating a more severe neurologic deficit. Twenty-two lost to follow-up in the surgical group and 15 in the medical group.

[i] The *P* value was calculated with the use of the nonparametric Wilcoxon test.

[j] χ^2 test.

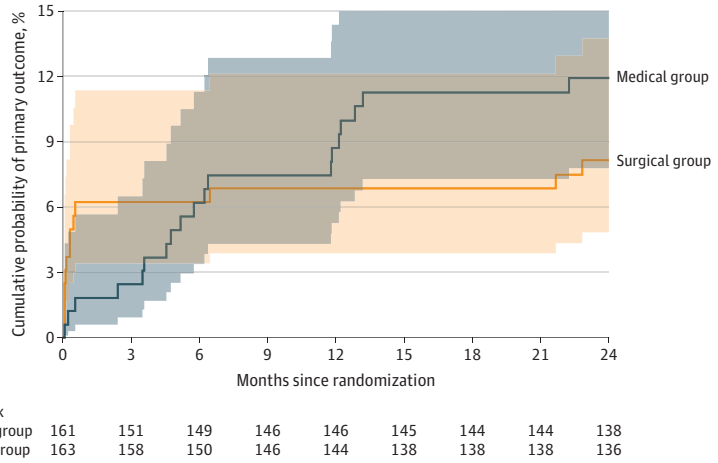
[k] Scores on the mRS range from 0 (no functional limitations) to 6 (death), with higher scores indicating more severe functional disability. A score of 2 or less indicates functional independence. Seventeen lost to follow-up in the surgical group and 14 in the medical group.

[l] There were 3 cases of asymptomatic cerebral infarction, 1 epidural hematoma, 1 hyperperfusion syndrome, and 1 subdural hematoma resulting in TIA.

did not differ significantly in patients who received EC-IC bypass surgery plus medical treatment compared with medical treatment alone. The results on all prespecified secondary outcomes were consistent with the primary result.

This trial demonstrated a lower rate of the primary outcome in the medical therapy alone group compared with previous studies. In this trial, the 2-year primary outcome rate was 12.3%, nearly half of that reported in COSS a decade ago (21.0%).[11]

Figure 2. Cumulative Probability of the Primary Outcome, According to Treatment Assignment



No. at risk									
Surgical group	161	151	149	146	146	145	144	144	138
Medical group	163	158	150	146	144	138	138	138	136

The primary outcome was a composite of stroke or death within 30 days or ipsilateral ischemic stroke beyond 30 days through 2 years after randomization. Nine patients lost to follow-up within 2 years in the surgical group and 6 patients in the medical group were treated as censored data. All other patients were followed up to event or 2 years. The median time of observation was 24.0 months (IQR, 24.0-24.0) for the surgical group and 24.0 months (IQR, 24.0-24.0) for the medical group. *P* = .39 for log-rank testing between the surgical group and medical group with the center information (site effect) as a stratification factor. The shading indicates 95% CI of the primary outcome.

Also, the rate was much lower than the anticipated 28% in the trial design.[17] Several reasons may have contributed to this discrepancy. First, this may have been due to improved efficacy of medical treatment, and similar trends of improved efficacy of medical treatment for other cerebrovascular diseases have been frequently reported. For example, for patients with asymptomatic carotid artery stenosis, ipsilateral ischemic stroke within 5 years in the medical group was lower in the SPACE-2 trial than that in the ACAS trial almost 30 years prior (3.1% vs 11.0%).[25,26] Also, in one study comparing stroke rates in the WASID and SAMMPRIS trials for patients with intracranial stenosis, a lower stroke rate at 12 months (12.6% vs 21.9%) was found in SAMMPRIS, which featured more intensive medical therapy targets.[27] Second, compared with COSS, the present study achieved an overall better control of risk factors for atherosclerosis such as hypertension and hyperlipidemia (eTable 1 in Supplement 3). Third, the imaging selection criteria may have identified less severe hemodynamic insufficiency than would be indicative of the target high-risk population. In contrast to COSS,[11] which relied on stage 2 hemodynamic failure on positron emission tomography imaging, the present study defined it on computed tomography perfusion with MTT longer than 4 seconds and rCBF ratio less than 0.95. However, in subgroup analysis, patients with MTT longer than 6 seconds (median of MTT) had higher primary outcome rates (Figure 3).

The perioperative stroke rate of 6.2% in this trial was substantially lower than that of 15% in COSS and that of 12% in the prior EC-IC Bypass Study.[9,11] In recent observational studies, the reported rate of perioperative stroke following bypass surgery for atherosclerotic vessel occlusion ranged from 4.3% to 8.9%,[12,28] similar to that of the present study. Besides the use of stricter criteria for surgeon certification in this trial compared with COSS,[17] intraoperative temporary occlusion time was also lower in this trial than COSS (21.0 vs 55.9 minutes [with stroke] or 45.4 minutes [without stroke]; eTable 4 in Supplement 3).[14] Strict periprocedural care implemented in this trial could be a further key factor in reducing perioperative risk. For example, the trial required monitoring intraprocedural P_{CO_2} and periprocedural blood pressure level, with protocol-defined targets (eTable 4 in Supplement 3). The inclusion criteria relating the time interval from the latest ischemic event to randomization was also different between this trial and COSS (12 months in CMOSS vs 120 days in COSS), but the actual time interval in CMOSS was comparable with that of COSS. Thus, this factor may not be a reason for the reduction of complication rates. This trial also limited enrollment to patients younger than 65 years compared with younger than 85 years in COSS, with the mean 52 vs 58 years of age. This may have contributed to the reduced risk in both groups of the trial, comparing this trial with the earlier study.

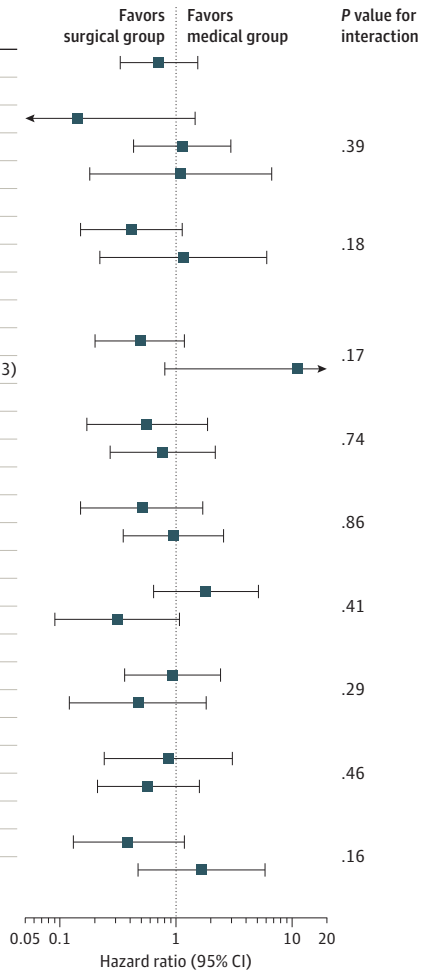
Despite the lower rates of perioperative risk than prior trials and the numerically lower rates of ipsilateral stroke beyond 30 days in the bypass surgery group in this trial, this study failed to show overall superiority of bypass surgery over medical treatment.[17] If bypass surgery is investigated in future trials, there are several factors to consider. Further refinement of patient selection may be needed to identify patients who could benefit most from bypass surgery. The subgroup of patients with MCA occlusion, who were not included in COSS, had a numerically lower rate of the primary outcome at 2 years compared with patients with ICA occlusion (5.8% [4/69] vs 11.0% [9/82]; *P* = .38; Figure 3), but the difference was not statistically significant and the test for interaction was not statistically significant (*P* for interaction = .29). The timing of bypass surgery may also need to be considered further; the perioperative risk of bypass surgery may be increased if surgery is performed shortly after the latest ischemic event, and the benefit of surgery may decrease in patients if surgery is performed much later after their event because hypoperfusion is compensated or medically managed. However, the optimal timing of bypass surgery is still unknown and may warrant further studies. In sum, future trials of EC-IC bypass may need larger sample sizes, refined patient selection (eg, MCA occlusion, MTT >6 seconds or rCBF ≤0.8), and longer follow-up time.

Limitations

This trial had several limitations. First, because sham surgery was not performed, there is the potential for bias in individual

Figure 3. Post Hoc Subgroup Analysis for the Primary Outcome[a]

	No./total (%)				
	Surgical group	Medical group	Incidence difference (95% CI)	Hazard ratio (95% CI)	*P* value for interaction
Overall	13/151 (8.6)	19/155 (12.3)	-3.6 (-10.1 to 2.9)	0.71 (0.33-1.54)	
Age, y					
<50	2/62 (3.2)	6/59 (10.2)	-6.6 (-15.1 to 1.9)	0.14 (0.01-1.46)	
50-60	9/67 (13.4)	9/64(14.1)	-0.9 (-11.9 to 10.1)	1.14 (0.43-2.97)	.39
>60	2/22 (9.1)	4/32 (12.5)	-3.4 (-19.4 to 12.6)	1.10 (0.18-6.69)	
Sex					
Male	7/116 (6.0)	15/124 (12.1)	-5.8 (-12.5 to 1.0)	0.41 (0.15-1.13)	
Female	6/35 (17.1)	4/31 (12.9)	3.8 (-13.2 to 20.7)	1.15 (0.22-6.06)	.18
Received medication prior to latest qualifying event					
Antiplatelet therapy					
Yes	9/125 (7.2)	18/140 (12.9)	-5.7 (-12.5 to 1.1)	0.49 (0.20-1.18)	
No	4/26 (15.4)	1/15 (6.7)	9.3 (-7.8 to 26.3)	11.15 (0.80-155.33)	.17
Lipid-lowering therapy					
Yes	4/36 (11.1)	10/57 (17.5)	-5.9 (-19.3 to 7.6)	0.56 (0.17-1.87)	
No	9/115 (7.8)	9/98 (9.2)	-1.5 (-8.7 to 5.7)	0.77 (0.27-2.18)	.74
Qualifying event					
Stroke	6/81 (7.4)	8/86 (9.3)	-2.2 (-10.0 to 5.6)	0.51 (0.15-1.70)	
TIA	7/70 (10.0)	11/69 (15.9)	-5.2 (-16.0 to 5.5)	0.95 (0.35-2.57)	.86
Latest ischemic event to randomization, wk					
≤6	7/47 (14.9)	8/47 (17.0)	-1.1 (-15.2 to 13.0)	1.81 (0.64-5.14)	
>6	6/104 (5.8)	11/108 (10.2)	-4.5 (-11.4 to 2.4)	0.31 (0.09-1.07)	.41
Qualifying artery					
Carotid artery	9/82 (11.0)	11/95 (11.6)	-0.8 (-9.7 to 8.1)	0.94 (0.36-2.42)	
Middle cerebral artery	4/69 (5.8)	8/60 (13.3)	-7.1 (-16.7 to 2.5)	0.47 (0.12-1.82)	.29
Mean transit time (qualifying side), s[b]					
≤6	5/67 (7.5)	7/80 (8.8)	-1.1 (-9.5 to 7.3)	0.86 (0.24-3.06)	
>6	7/76 (9.2)	12/69 (17.4)	-8.2 (-18.7 to 2.3)	0.57 (0.21-1.59)	.46
Relative cerebral blood flow[c]					
≤0.8	5/78 (6.4)	15/107 (14.0)	-7.4 (-15.5 to 0.7)	0.38 (0.13-1.18)	
>0.8	8/68 (11.8)	4/46 (8.7)	3.0 (-7.6 to 13.5)	1.66 (0.47-5.86)	.16



HR indicates hazard ratio; and TIA, transient ischemic attack.

[a] The primary outcome was a composite of stroke or death within 30 days or ipsilateral ischemic stroke beyond 30 days through 2 years after randomization.

[b] Mean transit time designates the mean time required for a contrast bolus to traverse the voxel and is measured in seconds. Mean transit time is inversely proportional to cerebral perfusion pressure and prolonged value indicates arterial stenosis or occlusion.

[c] Cerebral blood flow refers to the volume of blood flowing in a unit of brain mass during a unit of time (measured in mL/100 g/min). Relative cerebral blood flow denotes symptomatic side/asymptomatic side.

sites reporting potential end points for adjudication. Second, this study was conducted only in centers in China, and its generalizability to other populations outside of China is uncertain. Third, the enrolled population had a lower risk of events than that anticipated in the trial design, and the study may be underpowered to detect clinically relevant differences between groups. Fourth, the low-density lipoprotein cholesterol target level (<2.58 mmol/L [100 mg/dL]) according to guidelines at the time the trial began was relatively conservative compared with a lower low-density lipoprotein cholesterol target for those with large artery atherosclerosis in more recent trials. Even lower stroke rates in the medical therapy alone group may be observed in the future because only 38.1% of the medically treated patients reached the modern target low-density lipoprotein level of less than 70 mg/dL. Fifth, the enrollment of women was suboptimal and future research is needed to focus on the sex difference in atherosclerotic ICA or MCA occlusion and its prognosis.

Conclusions

Among patients with symptomatic ICA or MCA occlusion with hemodynamic insufficiency, the addition of bypass surgery to medical therapy did not significantly change the risk of stroke or death within 30 days or ipsilateral ischemic stroke beyond 30 days through 2 years. The findings do not support the addition of EC-IC bypass surgery to medical therapy for the treatment of patients with symptomatic atherosclerotic occlusion of the ICA or MCA.

ARTICLE INFORMATION

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Obtained funding: Jiao.
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Group Information: The Carotid and Middle Cerebral Artery Occlusion Surgery Study (CMOSS) investigators are listed in Supplement 4.

Data Sharing Statement: See Supplement 5.

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