Recurrent Hemispheric Stroke Syndromes in Symptomatic Atherosclerotic Internal Carotid Artery Occlusions: The Carotid Occlusion Surgery Study Randomized Trial

Fadi Nahab, MD [*]
Michael Liu, BS [*]
Haseeb A. Rahman, MD [*]
Srikant Rangaraju, MBBS [*]
Daniel Barrow, MD [*]
C. Michael Cawley, MD [*]
Robert L. Grubb, Jr, MD [‡]
Colin P. Derdeyn, MD [§]
Harold P. Adams, Jr, MD [§]
Tom O. Videen, PhD [¶]
M. Bridget Zimmerman, PhD [§]
William J Powers, MD [‖]
on behalf of the COSS Investigators

[*]Emory University, Atlanta, Georgia; [‡]Charleston, South Carolina; [§]University of Iowa, Iowa City, Iowa; [¶]Santa Fe, New Mexico; [‖]University of North Carolina, Chapel Hill, North Carolina

Correspondence:
Fadi Nahab, MD,
Emory University,
1365 Clifton Road, Clinic B, Suite 2200,
Atlanta, GA 30322.
Email: fnahab@emory.edu

Received, January 14, 2019.
Accepted, June 27, 2019.
Published Online, September 11, 2019.

BACKGROUND: There are limited data on outcomes of extracranial-intracranial (EC-IC) bypass in patients with recurrent hemispheric syndromes due to atherosclerotic internal carotid artery occlusion (AICAO).

OBJECTIVE: To compare clinical outcomes and efficacy of EC-IC bypass surgery in patients with and without recurrent hemispheric syndromes associated with AICAO in the Carotid Occlusion Surgery Study (COSS).

METHODS: In patients enrolled in the COSS trial, we compared baseline characteristics and clinical outcomes for participants with (rHEMI+) and without recurrent hemispheric ischemia (rHEMI−) prior to randomization into surgical vs medical groups. The primary outcome was all stroke and death from randomization through 30 d and ipsilateral ischemic stroke within 2 yr.

RESULTS: Of 195 randomized participants, 100 were rHEMI+ (50 in each group). Baseline characteristics between rHEMI+ and rHEMI− participants were similar except rHEMI+ were more likely to have had previous stroke prior to randomization (61% vs 20%, $P < .01$) and to have TIA as the entry event (59% vs 21%, $P < .01$). All primary endpoints were ipsilateral ischemic strokes. There were no significant differences in occurrence of the primary endpoint between nonsurgical and surgical participants in rHEMI+ (26.3% vs 22.4%, $P = .660$) and rHEMI− (18.9% vs 19.5%, $P = .943$). For nonsurgical participants, there was no significant difference in the primary endpoint for rHEMI+ vs rHEMI− patients ($P = .410$)

CONCLUSION: Patients with recurrent hemispheric stroke syndromes enrolled in the COSS trial did not show benefit from EC-IC bypass compared to medical treatment. Early aggressive risk factor measures should be prioritized to reduce recurrent strokes in these patients.

KEY WORDS: Stroke, Bypass, Carotid occlusion, Treatment

Neurosurgery 87:137–141, 2020 DOI:10.1093/neuros/nyz352 www.neurosurgery-online.com

Atherosclerotic internal carotid artery occlusion (AICAO) contributes to 15% to 25% of ischemic strokes in the anterior circulation.[1,2] Overall, patients with symptomatic AICAO, have a 2-yr risk of subsequent ipsilateral ischemic stroke of 10% to 15%, but this risk increases to 25% for those with severe hemodynamic impairment.[3,4] Medical and surgical management are both options for secondary stroke prevention. Medical management includes the use of antiplatelet therapy combined with aggressive risk factor control. Surgical options include extracranial-intracranial (EC-IC) arterial bypass for symptomatic AICAO and typically involves ipsilateral anastomosis of the superficial temporal

ABBREVIATIONS: AICAO, atherosclerotic internal carotid artery occlusion; **COSS,** Carotid Occlusion Surgery Study; **EC-IC,** extracranial-intracranial; **ICA,** internal carotid artery; **NIHSS,** National Institutes of Health Stroke Scale; **NINDS,** National Institute of Neurological Diseases and Stroke; **OEF,** oxygen extraction fraction; **PET,** positron emission tomography; **SS-QOL,** stroke-specific quality of life

artery to the middle cerebral artery thereby bypassing the occluded internal carotid artery (ICA).[4,5]

Early studies examining the efficacy of EC-IC bypass demonstrated no benefit to surgical bypass but failed to identify candidates with poor cerebral hemodynamics.[5] The Carotid Occlusion Surgery Study (COSS) evaluated recently symptomatic AICAO patients with hemodynamic cerebral ischemia and found that patients did not additionally benefit from EC-IC bypass surgery over medical therapy alone. It showed that the medical and surgical groups had similar rates of recurrent ipsilateral ischemic stroke and death during follow-up.[4] The RECON study, an ancillary study to COSS, also showed no benefit in cognitive improvement in those who received EC-IC bypass.[6]

The COSS trial enrolled participants who had a history of at least one transient ischemic attack (TIA) or ischemic stroke ipsilateral to the occluded ICA within the 120 d prior to randomization. However, it was not reported whether patients with recurrent hemispheric stroke syndromes prior to randomization (rHEMI+) had different clinical outcomes. The objective of our secondary analysis of the COSS was to determine whether patients with (rHEMI+) and without recurrent hemispheric stroke syndromes (rHEMI−) prior to randomization differed with respect to baseline characteristics, recurrent stroke rates, and the effect of (EC-IC) bypass.

METHODS

The COSS was a parallel-group, open-label, blinded adjudication treatment trial, which randomized 1:1 participants with recently symptomatic AICAO and hemodynamic cerebral ischemia to EC-IC arterial bypass surgery plus medical therapy or medical therapy alone. The study was done under the approval and supervision of a local IRB, the FDA, and the National Institute of Neurological Diseases and Stroke (NINDS). All participants signed consent forms to participate in the study. Detailed study inclusion and exclusion criteria, follow-up, and outcome measures have previously been reported.[4] Eligible patients had vascular imaging demonstrating complete occlusion of the ICA, TIA, or ischemic stroke in the territory of the occlusion within 120 d, positron emission tomography (PET) scans demonstrating increased oxygen extraction fraction (OEF), and arteriography to demonstrate occlusion as well as suitable arteries for grafting. The medical management group continued to receive their regular antithrombotic treatment by their physician and were held to risk factor targets of a blood pressure goal below 130/85, a low-density lipoprotein goal of below 100 mg/dL, a triglyceride goal below 150 mg/dL, and a hemoglobin A_1C goal below 7%. The primary endpoint for those who received surgery was a composite of stroke and death between surgery through 30 d after surgery and ipsilateral ischemic stroke within 2 yr of randomization. For those randomized to the medical group, the composite primary endpoint was all stroke and death from randomization through 30 d after randomization and ipsilateral ischemic stroke within 2 yr of randomization. Secondary endpoints included all stroke, disabling stroke, fatal stroke, death, National Institutes of Health Stroke Scale (NIHSS) score, modified Barthel index, modified Rankin Scale score, and stroke-specific quality of life (SS-QOL) score. Initial follow-up evaluation occurred between 30 to 35 d after randomization and a PET scan was performed for surgical patients between 30 and 60 d postsurgery. Subsequent follow-up occurred at 3-mo intervals for 2 yr and included history, examination, and Doppler examination for graft patency as applicable.[2]

For this post hoc analysis, we examined the subgroup of patients with (rHEMI+) and without (rHEMI−) recurrent ipsilateral hemispheric syndromes at the time of randomization into COSS. rHEMI+ was defined as any history of prior ipsilateral stroke or TIA as determined by the local investigator prior to the qualifying event into the study. The groups were compared based on their baseline characteristics as well as the primary and secondary endpoints as previously described.

Statistical Analysis

Baseline characteristics were compared using the Fisher exact test for categorical variables and Wilcoxon rank-sum tests for continuous variables. For the primary endpoint, rates were based on product limit estimates of 2-yr rates and their standard errors. Participants were censored at their last follow-up visit. All randomized participants were analyzed in the treatment group to which they were initially randomized. Secondary endpoints were analyzed using the same methods. For dichotomized outcomes, differences between treatments were compared using Fisher exact test and summary SS-QOL scores were compared using a t test. SAS version 9.2 (SAS Institute; Cary, North Carolina) was used in the analyses.

RESULTS

All 195 participants from the COSS trial were included in this study including 100 who were rHEMI+ and 95 rHEMI−. Follow-up for the primary endpoint until occurrence, 2 yr, or end of trial was 99% complete. Of those in the rHEMI+ subgroup, 50 were randomized into the surgical group and 50 into the nonsurgical group. Of those in the rHEMI− subgroup, 47 were randomized into the surgical and 48 into the nonsurgical group. Baseline characteristics were similar between rHEMI+ and rHEMI− participants except that rHEMI+ participants were more likely to have had a previous stroke prior to entry (61 vs 20%, $P < .01$) and a TIA (vs stroke) as the entry event (59 vs 21%, $P < .01$), and shorter median days from entry event to randomization ($P = .04$) (Table 1).

All primary endpoints were ipsilateral ischemic strokes. There were no significant differences in the primary endpoint between nonsurgical and surgical participants with rHEMI (26.3 vs 22.4%, $P = .66$) or without rHEMI (18.9 vs 19.5%, $P = .94$). When comparing the primary endpoint between those receiving nonsurgical treatment, there was no difference between the groups (rHEMI+ 26.3 vs rHEMI− 18.9%, $P = .41$). When comparing the primary endpoint between those randomized to surgical treatment, there was no difference between the groups (rHEMI+ 22.4 vs rHEMI− 19.5%, $P = .73$) (Table 2).

Secondary endpoints including any stroke, fatal stroke, disabling stroke and deaths were similar between surgical and nonsurgical groups in both rHEMI+ and rHEMI− subgroups

TABLE 1. Baseline Characteristics of the Cohort

	Recurrent hemispheric syndrome at baseline		No recurrent hemispheric symptom at baseline		
	Surgical	Nonsurgical	Surgical	Nonsurgical	*P* value
Participants, No.	50	50	47	48	
Age, mean (SD), years	58.9 (7.6)	57.1 (9.6)	57.8 (10.4)	59.0 (8.4)	.68
Male, No. (%)	31 (62)	35 (70)	38 (81)	26 (54)	.04
Race White, No. (%)	47 (94)	47 (94)	41 (87)	45 (94)	.64
Hypertension, No. (%)	40/49 (82)	43 (86)	36 (77)	34/47 (72)	.37
Hyperlipidemia, No. (%)	42/49 (86)	46 (92)	37 (79)	40/47 (85)	.33
Diabetes mellitus, No. (%)	10/49 (20)	14 (28)	11 (23)	9/47 (19)	.73
Cigarette smoking, No. (%)	(n = 49, 1 missing)				.38
Current	17 (35)	24 (48)	16 (34)	13 (28)	
Former	30 (61)	22 (44)	26 (55)	29 (62)	
Previous myocardial infarction, No. (%)	5 (10)	11 (22)	6 (13)	3 (6)	.11
Previous stroke, No. (%)	33/48 (69)	27 (54)	11 (23)	8/46 (17)	<.01
Entry event type, No. (%)					<.01
Stroke	17 (35)	23 (46)	35 (74)	39 (81)	
Transient ischemic attack	32(64)	27(54)	12(26)	8(17)	
Unknown	1(2)			1(2)	
Entry event side, No. (%)					.55
Left	23 (46)	28 (56)	20 (43)	25 (52)	
Right	27(54)	22(44)	27(57)	23(48)	
Entry event to randomization, median (IQR), days	62 (59)	60 (60)	79 (84)	86 (50)	.04
PET ratio, median (IQR)	1.21 (0.12)	1.22 (0.14)	1.21 (0.15)	1.21 (0.13)	.66
Modified Rankin score, median (IQR)	1.0 (1.0)	1.0 (1.0)	1.0 (2.0)	1.0 (1.0)	.87
NIHSS, median (IQR)	1.0 (3.0)	1.5 (3.0)	1.0 (3.0)	1.0 (3.0)	.73
SSQoL (Summary), mean (SD)	3.55 (0.89)	3.60 (0.84)	3.92 (0.83)	3.82 (0.78)	.10
Systolic blood pressure, mean (SD), mm Hg	133 (16)	138 (19)	134 (15)	140 (21)	.13
Diastolic blood pressure, mean (SD), mm Hg	77 (10)	77 (11)	76 (11)	78 (9)	.71
LDL-cholesterol, median (IQR), (mg/dL)	100 (58) (n = 35)	98 (41) (n = 36)	94 (55) (n = 41)	100 (34) (n = 33)	.96
Hemoglobin A1C, mean (SD), (%)	5.8 (0.6) (n = 38)	5.9 (0.6) (n = 41)	5.6 (0.9) (n = 45)	5.7 (0.6) (n = 33)	.46

TABLE 2. Primary Study Endpoints. Analysis for 2-yr Stroke Rate-Probability Distributions of Time to Primary Endpoint (Stroke Rate) after 24 mo

	Medical group	*P* value	Surgical group	*P* value
Recurrent hemispheric symptoms at baseline	n = 50 0.263 (SE 0.066)	.410	n = 50 0.224 (SE 0.060)	.730
No recurrent hemispheric symptoms at baseline	n = 48 0.189 (SE 0.061)		n = 47 0.195 (SE 0.059)	

(Tables 3 and 4). Disability scores at last follow-up and mean quality of life measures were also similar between surgical and nonsurgical groups in both rHEMI+ and rHEMI− groups.

DISCUSSION

The COSS results showed no benefit for EC-IC bypass in patients with recent symptomatic AICAO.[4,6] The COSS was terminated early based on a futility analysis. Based on the observed rates until that point, there was a probability of only 2% that the study would have rejected the null hypothesis if all 372 originally scheduled participants had finished 2-yr follow-up. Interpretation of the study is limited by the relatively small number of outcome events. The 95% confidence bounds of the difference in the primary endpoint 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 endpoints for adjudication. This did not appear to have occurred, given that the number of reported events adjudicated not to be primary or secondary endpoints was 6 in the surgical group and 4 in the nonsurgical group. The choice of the count-based OEF ratio for the COSS eligibility was based on receiver operating curve and cost effectiveness analysis. We have shown that the count-based OEF ratio is superior to the use of an absolute value.

TABLE 3. Secondary Endpoints for rHEMI+ Patients

Secondary endpoints	Surgical group (n = 50)		Nonsurgical group (n = 50)		Surgical-nonsurgical	
	Number of events	Estimated rate (95% CI)	Number of events	Estimated rate (95% CI)	Difference (95% CI)	*P* value
Any stroke	11	22.4 (10.7, 34.1)	12	26.3 (13.4, 39.2)	−3.9 (−21.4, 13.5)	.66
Fatal stroke	0	0	1	2.5 (0, 7.3)	−2.5 (−7.3, 2.3)	.31
Disabling stroke	2	4.0 (0, 9.4)	1	2.5 (0, 7.3)	1.5 (−5.8, 8.8)	.68
Deaths	0	0 (0.0, 7.1)	4	8.0 (2.2, 19.2)	−8.0 (−28.0, 12.5)	.12
Any stroke or death	11	22.4 (10.7, 34.1)	14	32.2 (17.9, 46.6)	−9.8 (−28.3, 8.7)	.30
Modified Rankin score 0 to 1	29	58.0 (44.3, 71.7)	21	42.0 (28.3, 55.7)	16.0 (−3.4, 35.4)	.11
Modified Rankin score 0 to 2	39	78.0 (66.5, 89.5)	42	84.0 (73.8, 94.2)	−6.0 (−21.3, 0.3)	.44
Modified Barthel scale 19 to 20	39	78.0 (66.5, 89.5)	39	78.0 (66.5, 89.5)	0.0 (−16.2, 20.3)	1.0
Summary SSQoL, mean		3.63 (3.34, 3.92)		3.55 (3.28, 3.81)	0.08 (−0.31, 0.47)	.68

TABLE 4. Secondary Endpoints for rHEMI− Patients

Secondary endpoints	Surgical group (n = 47)		Nonsurgical group (n = 48)		Surgical-nonsurgical	
	Number of events	Estimated rate (95% CI)	Number of events	Estimated rate (95% CI)	Difference (95% CI)	*P* value
Any stroke	11	24.3 (11.7, 36.9)	11	25.0 (12.1, 37.9)	− 0.7 (−18.7, 17.4)	.94
Fatal stroke	1	2.1 (0, 6.3)	1	2.2 (0, 6.4)	− 0.04 (−5.9, 5.9)	.99
Disabling stroke	3	7.3 (0,15.3)	1	2.2 (0, 6.4)	5.1 (−3.9, 14.1)	.27
Deaths	1	2.1 (0.05, 11.3)	1	2.1 (0.05, 11.1)	0.0 (−19.9, 19.9)	1.0
Any stroke or death	11	24.3 (11.7, 36.9)	11	25.0 (12.1, 37.9)	− 0.7 (−18.7, 17.4)	.94
Modified Rankin score 0 to 1	25	53.2 (38.9, 67.5)	23	47.9 (33.8, 62.0)	5.3 (−14.8, 25.4)	.61
Modified Rankin score 0 to 2	41	87.2 (77.7, 96.8)	39	81.2 (70.2, 92.3)	6.0 (−8.6, 20.6)	.42
Modified Barthel scale 19 to 20	39	83.0 (72.2, 93.7)	39	81.3 (70.2, 92.3)	1.7 (−13.7, 17.1)	.83
Summary SSQoL, mean		3.82 (3.52, 4.11)		3.69 (3.46, 3.92)	0.13 (−0.24, 0.50)	.49

The eligibility criteria used in the COSS successfully identified a group of patients who were at very high 2 yr risk of 22.7% for subsequent ipsilateral stroke on medical therapy. The COSS was designed with a 2-yr endpoint. Data from other trials of medically treated symptomatic large artery atherosclerosis show a major decrease in stroke rate after 2 yr. Thus, it is not valid to assume that the event rate observed during the first 2 yr would continue and thus create a significant difference if the study had been continued for 5 yr. Participants in the COSS were randomized a mean of 73.5 d after qualifying event. In the nonsurgical group time from qualifying event was not a predictor of subsequent stroke nor, as reported here (Table 2), was the presence of recurrent hemispheric events.[4,7]

We hypothesized that a subgroup of COSS participants with recurrent hemispheric stroke symptoms prior to randomization would be more likely to have future stroke events on medical therapy. However, our study found similar 2 yr stroke rates in the medical groups of rHEMI+ and rHEMI− patients suggesting that a history of recurrent stroke symptoms did not portend a higher risk of future events in COSS. Additionally, we found no surgical benefit for rHEMI+ and rHEMI− participants compared with the medical group for all of the prespecified primary and secondary endpoints.

Our study has important implications on the management of rHEMI+ patients with AICAO: rHEMI+ patients did not have significantly higher rates of future strokes than rHEMI− patients and did not benefit from surgical bypass. Given that COSS participants who did not achieve a mean blood pressure ≤130/85 mm Hg (COSS target blood pressure goal) had significantly higher rates of ipsilateral ischemic strokes during follow-up than those who achieved the goal (HR 3.742, 95% CI 1.065-13.153, $P = .027$), our results further highlight the importance of aggressive risk factor control including blood pressure management.[8]

CONCLUSION

Patients with recurrent hemispheric stroke syndromes enrolled in the COSS trial did not show benefit from EC-IC bypass

compared to medical treatment alone. Early aggressive risk factor measures should be prioritized to reduce recurrent strokes in these patients given the lack of benefit from surgical bypass.

Disclosures

This study was supported by USPHS grants NS39526, NS42157, and NS41895 from the National Institutes of Neurological Disorders and Stroke. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Powers WJ. Atherosclerotic carotid artery occlusion. *Curr Treat Options Cardio Med*. 2003;5(6):501-509.
2. Flaherty ML, Flemming KD, McClelland R, Jorgensen NW, Brown RD, Jr. Population-based study of symptomatic internal carotid artery occlusion: incidence and long-term follow-up. *Stroke*. 2004;35(8):e349-e352.
3. Grubb RL, Jr, Derdeyn CP, Fritsch SM, et al. Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. *JAMA*. 1998;280(12):1055-1060.
4. Powers WJ, Clarke WR, Grubb RL, Videen TO, Adams HP, Derdeyn CP. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia the carotid occlusion surgery study randomized trial. *JAMA*. 2011;306(18):1983-1992.
5. Barnett HJ, Peerless SJ, Fox AJ, et al. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. *N Engl J Med*. 1985;313(19):1191-1200.
6. Marshall RS, Festa JR, Cheung YK, et al. Randomized Evaluation of Carotid Occlusion and Neurocognition (RECON) trial: main results. *Neurology*. 2014;82(9):744-751.
7. Powers WJ, Clarke WR, Adams HP, Jr, Derdeyn CP, Grubb RL, Jr. Commentary: extracranial intracranial bypass for stroke in 2012: response to the critique of the carotid occlusion surgery study "It was déjà vu all over again". *Neurosurgery*. 2012;71(3):E772-E776.
8. Powers WJ, Clarke WR, Grubb RL, Jr, Videen TO, Adams HP, Derdeyn CP. Lower stroke risk with lower blood pressure in hemodynamic cerebral ischemia. *Neurology*. 2014;82(12):1027-1032.

Acknowledgments

The authors thank all the people who worked on COSS and all the patients who volunteered to participate.