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Endovascular Therapy for Acute Ischemic Stroke With Occlusion of the Middle Cerebral Artery M2 Segment

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IMPORTANCE Randomized clinical trials have shown the superiority of endovascular therapy (EVT) compared with best medical management for acute ischemic strokes with large vessel occlusion (LVO) in the anterior circulation. However, of 1287 patients enrolled in 5 trials, 94 with isolated second (M2) segment occlusions were randomized and 51 of these received EVT, thereby limiting evidence for treating isolated M2 segment occlusions as reflected in American Heart Association guidelines.

OBJECTIVE To evaluate EVT safety and effectiveness in M2 occlusions in a cohort of patients with acute ischemic stroke.

DESIGN, SETTING, AND PARTICIPANTS This multicenter retrospective cohort study pooled patients with acute ischemic strokes and LVO isolated to M2 segments from 10 US centers. Patients with acute ischemic strokes and LVO in M2 segments presenting within 8 hours from their last known normal clinical status (LKN) from January 1, 2012, to April 30, 2015, were divided based on their treatment into EVT and medical management groups. Logistic regression was used to compare the 2 groups. Univariate and multivariate analyses evaluated associations with good outcome in the EVT group.

MAIN OUTCOMES AND MEASURES The primary outcome was the 90-day modified Rankin Scale score (range, 0-6; scores of 0-2 indicate a good outcome); the secondary outcome was symptomatic intracerebral hemorrhage.

RESULTS A total of 522 patients (256 men [49%]; 266 women [51%]; mean [SD] age, 68 [14.3] years) were identified, of whom 288 received EVT and 234 received best medical management. Patients in the medical management group were older (median [interquartile range] age, 73 [60-81] vs 68 [56-78] years) and had higher rates of intravenous tissue plasminogen activator treatment (174 [74.4%] vs 172 [59.7%]); otherwise the 2 groups were balanced. The rate of good outcomes was higher for EVT (181 [62.8%]) than for medical management (83 [35.4%]). The EVT group had 3 times the odds of a good outcome as the medical management group (odds ratio [OR], 3.1; 95% CI, 2.1-4.4; $P < .001$) even after adjustment for age, National Institute of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early Computed Tomographic Score (ASPECTS), intravenous tissue plasminogen activator treatment, and time from LKN to arrival in the emergency department (OR, 3.2; 95% CI, 2-5.2; $P < .001$). No statistical difference in symptomatic intracerebral hemorrhage was found (5.6% vs 2.1% for the EVT group vs the medical management group; $P = .10$). The treatment effect did not change after adjusting for center (OR, 3.3; 95% CI, 1.9-5.8; $P < .001$). Age, NIHSS score, ASPECTS, time from LKN to reperfusion, and successful reperfusion score of at least 2b (range, 0 [no perfusion] to 3 [full perfusion with filling of all distal branches]) were independently associated with good outcome of EVT. A linear association was found between good outcome and time from LKN to reperfusion.

CONCLUSIONS AND RELEVANCE Although a randomized clinical trial is needed to confirm these findings, available data suggest that EVT is reasonable, safe, and effective for LVO of the M2 segment relative to best medical management.

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Editorial page 1277

Supplemental content

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Five recently published randomized clinical trials (RCTs)[1-5] demonstrated the superiority of endovascular therapy (EVT) compared with best medical management, including intravenous tissue plasminogen activator (IV tPA) therapy for acute ischemic strokes with large vessel occlusion (LVO) in the anterior circulation. However, the RCTs' inclusion criteria focused on proximal occlusions involving the distal internal carotid artery and proximal (first segment [M1]) middle cerebral artery (MCA). Patients with more distal occlusions in the second-order branches (M2) of the MCA, however, were underrepresented in the trials. ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT [Computed Tomography] to Recanalization Times),[2] SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke),[4] and REVASCAT (Randomized Trial of Revascularization With Solitaire FR Device vs Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset)[5] restricted enrollment to patients with more proximal occlusions, although a few patients were misclassified as having M1 segment occlusion by the enrolling center and were subsequently adjudicated by the core laboratory as having M2 segment occlusion. MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands)[1] and EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-arterial)[3] enrolled only a few patients with distal occlusions. Of 1287 patients enrolled in the 5 trials, only a total of 94 patients were randomized; 51 of these patients received EVT. Evidence from RCTs regarding the benefit of EVT is therefore lacking for M2 segment occlusions, as reflected in the recent American Heart Association guidelines.[6]

Competing issues highlight the uncertainty of how to best treat more distal occlusions, which represent an important subgroup of patients with LVO. Concerns have been raised about the procedural safety of intervention in smaller-caliber vessels, especially that data support the concept of more distal occlusions responding better to intravenous thrombolysis.[7] However, medical management, including administration of intravenous thrombolytics, results in lower reperfusion rates than EVT for such large-artery occlusions, potentially leading to large infarct volumes with severe neurologic deficits. More data are needed to address whether the risk of not intervening for an M2 segment occlusion outweighs the risks of treating an M2 segment occlusion with EVT. We sought to evaluate the safety and treatment effect of EVT compared with best medical management in patients with acute ischemic stroke and LVO in the anterior circulation isolated to the M2 segments.

Key Points

Question Is endovascular therapy (EVT) superior to best medical management of occlusions of the second (M2) segment of the middle cerebral artery?

Findings In this retrospective pooled analysis of 522 patients, higher proportions of patients treated with EVT achieved good clinical outcomes measured as independence at 90 days (62.8%) than did those treated with best medical management (35.4%), a statistically significant difference.

Meaning Endovascular therapy is effective and may be superior to best medical management in occlusions of the M2 segment of the middle cerebral artery.

Methods

Study Design, Setting, and Participants

A multicenter retrospective cohort was pooled from 10 participating academic US stroke centers (listed in eTable 1 in the Supplement). Patients with acute ischemic stroke and LVO isolated to M2 segments who presented within 8 hours from the last known normal clinical status (LKN) from January 1, 2012, to April 30, 2015, were included. The start of the M2 segment of the MCA was defined as the vertical segment lying within the mesial margin of the sylvian fissure as identified on the coronal CT angiogram, anterior-posterior projection of the magnetic resonance angiogram, or anterior-posterior conventional angiogram as read and adjudicated locally by the participating center (eFigure in the Supplement). The study was approved by the institutional review boards of the 10 participating centers (University of Texas, Houston; Riverside Methodist Hospital, Columbus, Ohio; Texas Stroke Institute, Dallas; Kaiser Permanente, Los Angeles, California; Cleveland Clinic, Cleveland, Ohio; University of Tennessee, Memphis; Saint Louis University, St Louis, Missouri; Tulane University, New Orleans, Louisiana; Kansas University, Kansas City; and WellStar Kennestone, Marietta, Georgia), which determined that informed consent was not required for this retrospective study.

Study Treatment and Intervention

Patients were divided based on their treatment into EVT and best medical management groups. Best medical management included IV tPA therapy in patients presenting within the first 4.5 hours from the LKN when appropriate. Endovascular treatment included mechanical thrombectomy by means of stent retrievers or aspiration techniques; intra-arterial thrombolytics were given in some cases.

Demographics, Variables, and Measurements

Information on baseline demographics, vascular risk factors, admission blood glucose level, and National Institute of Health Stroke Scale (NIHSS) score (range, 0-42, with higher scores indicating severe stroke) were obtained from the prospectively collected stroke registries of the different centers. Other clinical end points obtained included symptomatic intracerebral hemorrhage (defined as a parenchymal hematoma grade 2 associated with worsening neurologic status thought to be related to the hematoma), neurologic deterioration (defined as a ≥4-point increase in the NIHSS score), and functional outcome at 90 days as measured by modified Rankin Scale (range, 0-6, with lower scores indicating better outcomes).[8] Type of

Table 1. Patient Baseline Characteristics

Characteristic	Study Group EVT (n = 288)	Medical Management (n = 234)	*P* Value
Age, y			
Mean (SD)	66 (15)	70 (14)	.002
Median (IQR)	68 (56-78)	73 (60-81)	.003
Male sex, No. (%)	144 (50)	112 (47.9)	.60
NIHSS score, median (IQR)[a]	16 (11-20)	15 (11-20)	.90
Clinical history, No. (%)			
Hypertension	216 (75)	178 (76.1)	.50
Hyperlipidemia	120 (41.7)	77 (32.9)	.30
Diabetes	60 (20.8)	66 (28.2)	.40
Atrial fibrillation	103 (35.8)	80 (34.2)	.70
Current smoker	66 (22.9)	51 (21.8)	.90
ASPECTS, median (IQR)[b]	9 (7-10)	9 (7-9)	.90
IV tPA treatment, No. (%)	172 (59.7)	174 (74.4)	.001
Time metrics, median (IQR), min			
From LKN to arrival at the ED	158 (73-262)	86 (48-190)	.001
From LKN to GP	270 (181-380)	NA	NA
From CT to GP	74 (52-111)	NA	NA
From GP to recanalization	41 (32-55)	NA	NA

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomographic Score; CT, computed tomography; ED, emergency department; EVT, endovascular therapy; GP, groin puncture; IQR, interquartile range; IV tPA, intravenous tissue plasminogen activator; LKN, last known normal clinical status; NA, not applicable; NIHSS, National Institute of Health Stroke Scale.

[a] Scores range from 0 to 42, with higher scores indicating severe stroke.

[b] Scores range from 0 to 10, with higher scores indicating a normal CT finding.

intra-arterial thrombolytic, duration of the procedure, and time to recanalization were also reported from the respective centers' databases.

Imaging Analysis

Early ischemic changes were measured by the Alberta Stroke Program Early Computed Tomographic Score (ASPECTS) on non-contrast-enhanced CT head scans. For recanalization, the modified Thrombolysis in Ischemic Stroke score was used; successful reperfusion (partial and complete) was defined as a modified score of 2b or higher (range, 0 [no perfusion] to 3 [full perfusion with filling of all distal branches).[9] The CT and angiographic images were adjudicated locally at the facility of treatment.

Study Outcomes

The primary outcome consisted of clinical functional outcomes measured by the 90-day modified Rankin Scale score (good outcome was defined as a modified Rankin Scale score of 0-2). A secondary outcome was the rate of symptomatic intracranial hemorrhage. Other secondary outcomes included rates of asymptomatic hemorrhage and reperfusion in the EVT group measured by the modified Thrombolysis in Ischemic Stroke score.

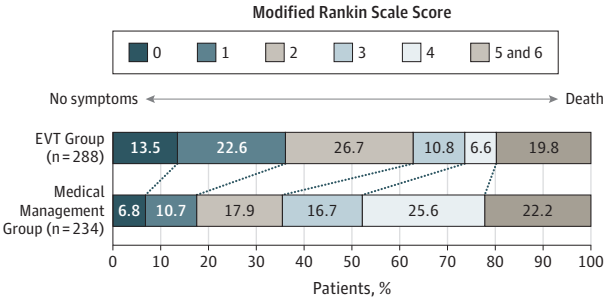
Statistical Analysis

The population's mean (SD), median (interquartile range [IQR]), and dispersion characteristics are described as appropriate. We used the unpaired, 2-tailed *t* test and Mann-Whitney test to compare mean and median data, respectively, between groups. Categorical variables were evaluated using the χ^2 test or Fisher exact test where appropriate. A logistic regression model compared treatment effect in the 2 groups, with adjustment for clinical and radiographic variables based on their clinical significance or statistical differences between the 2 groups. Also, adjustment was made for the center given the potential confounding arising from different treatment patterns (EVT vs best medical management) at different centers. Univariate and multivariate analyses were completed to evaluate the association with good outcome in the EVT group. Also, we stratified outcome in the EVT group based on quartiles of time from LKN finding to recanalization (in minutes) given the reported importance of time from onset to reperfusion in the previous trials.

Results

A total of 522 patients (256 men [49%]; 266 women [51%]; mean [SD] age, 68 [14.3] years) met the inclusion criteria, of whom 288 received EVT and 234 received best medical management. eTable 1 in the Supplement shows patient enrollment and treatment (EVT vs medical management) per center. **Table 1** shows baseline characteristics. Patients in the medical management group were older (median [IQR] age, 73 [60-81] vs 68 [56-78] years; *P* = .003), had higher rates of IV tPA treatment (74.4% vs 59.7%; *P* = .001), and presented earlier to the emergency department (median [IQR], 86 [48-190] vs 158 [73-262] minutes; *P* = .001); otherwise, the 2 groups were balanced. The degrees of early ischemic changes on initial non-contrast-enhanced CT measured by the ASPECTS score were similar in both groups, with medians of 9 (IRQ, 7-10 for the EVT group and 7-9 for the medical management group) (scores range from 0-10, with higher scores indicating a normal CT finding). Mechanical thrombectomy with stent retrievers (with or without balloon guide or with or without aspiration) was used in 256 cases (88.9%), whereas aspiration alone was used in 32 cases (11.1%) as a primary technique. More patients treated with EVT had better 90-day clinical outcomes compared with the medical management group (62.8% vs 35.4%) (**Figure 1**, **Table 2**, and **Table 3**). The EVT-treated patients had 3 times the odds of good outcomes compared with patients who received medical management (odds ratio [OR], 3.1; 95% CI, 2.1-4.4; *P* < .001). The

Figure 1. Modified Rankin Scale Scores at 90 Days



Outcomes are compared for the endovascular therapy (EVT) vs medical management groups.

Table 2. Patient Clinical Outcome Rates Measured by the Modified Rankin Scale (mRS) at 90 Days

	Study Group, No. (%) of Patients	
mRS Score[a]	EVT (n = 288)	Medical Management (n = 234)
0	39 (13.5)	16 (6.8)
1	65 (22.6)	25 (10.7)
2	77 (26.7)	42 (17.9)
3	31 (10.8)	39 (16.7)
4	19 (6.6)	60 (25.6)
5 and 6	57 (19.8)	52 (22.2)

Abbreviation: EVT, endovascular therapy.

[a] A score of 0 indicates no symptoms; 1, some symptoms but no disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death. An mRS score of 0 to 2 accounts for interdependency and is considered a good outcome.

treatment effect was maintained even after adjustment for age, NIHSS score, ASPECTS, IV tPA treatment, and time from LKN to arrival at the emergency department (OR, 3.2; 95% CI, 2-5.2; $P < .001$). The treatment effect did not change after adjusting for center (OR, 3.3; 95% CI, 1.9-5.8; $P < .001$). Although the rate of symptomatic intracranial hemorrhage was higher in the EVT group compared with the medical management group (5.6% vs 2.1%), this difference did not reach statistical significance ($P = .10$), as depicted in Table 3. Also, no difference in asymptomatic hemorrhage rates was seen (EVT group, 5.2%; medical management group, 7.3%; $P = .40$). Younger age, lower admission NIHSS score, higher ASPECTS, shorter time from LKN to reperfusion, and successful reperfusion (modified Thrombolysis in Ischemic Stroke score, ≥2b) were independently associated with good outcomes in the EVT group (eTable 2 in the Supplement). We found a linear association between good outcomes and time from LKN finding to reperfusion (**Figure 2**). Furthermore, rates of symptomatic intracranial hemorrhage and death rates were also similar to those from the previous RCTs.[1-5]

Discussion

Endovascular therapy for acute ischemic stroke due to LVO in the anterior circulation has been shown in 5 RCTs[1-5] to improve patients' clinical outcomes and reduce mortality rates relative to best medical management, including thrombolysis with IV tPA. These studies enrolled a much higher proportion of patients with proximal occlusions involving only distal internal carotid artery and proximal MCA (M1 segment) compared with distal MCA (M2 segment) occlusions, which leaves the question of best management for patients with M2 segment occlusions open because the relative effect size for treatment and safety of these more distal occlusions with EVT is not as well understood. The benefit of EVT remains uncertain even after the individual patient data-pooled meta-analysis from the 5 RCTs,[10] with the adjusted ORs showing no significance (OR, 1.28; 95% CI, 0.51-3.21). These results could be attributed to the underpowered small sample size of patients pooled from the trials because of the trials' aforementioned inclusion criteria, which further highlights the need for more data on this important subpopulation.

Rates of good outcomes for EVT in our data set are higher compared with those of patients with M2 segment occlusions from the recent trials (62.8% vs 49%). This difference could be caused by the latter representing more proximal M2 segment occlusions than in our cohort because those were misclassified as M1 segment occlusions at the enrolling site.

Treating physicians face uncertainty about the effectiveness of EVT in these patients and whether IV tPA treatment alone would suffice. In addition, they face concerns about complications of thrombectomy due to the smaller-caliber vessel size and technical difficulties with access to more distal clots. We attempted to address this population by pooling data from 10 academic centers that had treated patients with EVT or medical management alone. Our results support the benefit of EVT over medical management alone. Moreover, although rates of symptomatic intracranial hemorrhage were higher in the EVT group, this numerical difference was not statistically significant, which supports the safety profile of EVT for MCA M2 segment occlusions. Although our study involved a different patient population, our results are consistent with those of distal internal carotid artery and M1 occlusions in the recent trials.[1-5]

Consistent with prior published data, we also found that younger age, lower stroke severity score, better imaging profiles with smaller baseline infarcts, and fast, successful reperfusion were factors associated with a better EVT effect. Our study shows a linear association between a good clinical outcome and the time from the stroke ictus to reperfusion. Other recent studies attempted to address the question of EVT effectiveness in this subpopulation,[11,12] but they lacked a concurrent comparison group that received medical management,[11,12] included small samples of patients with M2 segment occlusions (54 and 50 patients), and in 1 case involved a single-center experience.[12]

Patients in our pooled data have high median NIHSS scores, which can be caused by multiple factors. These factors include possible clot migration from the M1 segment to the M2 segment secondary to IV tPA treatment or autologous clot lysis with involvement of the basal ganglia infarction during tran-

Table 3. Patient Clinical and Radiographic Outcomes

Outcome	Study Group		*P* Value	OR (95% CI)	
	EVT (n = 288)	Medical Management (n = 234)		Unadjusted	Adjusted[a]
Primary outcomes					
90-d mRS score, median (IQR)[b]	2 (1-4)	3 (2-4)	.001	3.1 (2.1-4.4)	3.2 (2-5.2)
90-d mRS score 0-2, No. (%)[b]	181 (62.8)	83 (35.4)	.001	NA	NA
mTICI score ≥2b, No. (%)[c]	225 (78)	NA	NA	NA	NA
Secondary outcomes, No. (%)					
Symptomatic ICH	16 (5.6)	5 (2.1)	.10	NA	NA
Asymptomatic ICH	15 (5.2)	17 (7.3)	.40	NA	NA
Neurologic worsening	26 (9)	33 (14.1)	.10	NA	NA

Abbreviations: EVT, endovascular therapy; ICH, intracerebral hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; NA, not applicable; OR, odds ratio.

[a] Adjustment was made for age, National Institute of Health Stroke Scale score, Alberta Stroke Program Early Computed Tomographic Score, intravenous tissue plasminogen activator treatment, and time from last known normal clinical status finding to arrival for treatment.

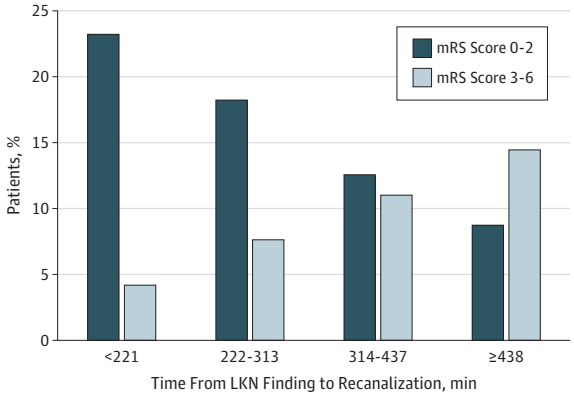
[b] Scores range from 0 to 6, with lower scores indicating better outcomes.

[c] A score of 0 indicates no perfusion; 1, minimal perfusion; 2a, reperfusion of less than half of previously occluded territory; 2b, reperfusion of more than half of previously occluded territory; and 3, complete reperfusion.

sient M1 segment occlusion, leading to worse clinical symptoms despite recanalization. Also, the anatomical asymmetry in the size of the M2 segments with the anterior or the posterior trunk may supply most of the MCA territory. Moreover, the inherent bias in the NIHSS toward eloquent areas supplied by the anterior division of the MCA, particularly in the dominant hemisphere where the motor strip and receptive language areas are affected, can lead to significant deficits and higher NIHSS scores. Stroke severity in our cohort is comparable to severity reported in recent studies.[12]

Our study has limitations. Despite the inherent limitations of the retrospective design, the 2 treatment groups were mostly similar at baseline. Patients in the medical management group had a higher rate of tPA treatment and presented earlier than patients in the EVT group, which would have biased the results, if any, toward a lower EVT effect. The patients in our cohort were from 10 centers with different EVT protocols; selection of patients for EVT and the devices used for thrombectomy were different and based on institutional protocols. These differences could have resulted in selection bias because patients who were more likely to benefit from EVT were the ones treated with the intervention. Although ASPECTS were similar between groups, more advanced image modalities, such as CT or magnetic resonance perfusion images, might have guided treatment choice. We could not report the proportions of those methods used, which places another limitation on our study. Although we used a unified anatomical definition of the M2 segment owing to the lack of a central reading, the possibility for misclassifications of the occluded segment of the MCA by the different centers, similar to what occurred in the recent RCTs, is a potential limitation. In addition, patients were not randomized between medical management and EVT; thus, we could not account for the unmeasured covariates in our analysis. However, the data from this study are derived from centers actively pursuing EVT and therefore reflect real-world situations. Although the difference in symptomatic hemorrhage rate was not statistically significant, it could have been of clinical significance; overall, however, the study findings support the safety of EVT in this patient population.

Figure 2. Clinical Outcomes of Patients in the Endovascular Therapy Group Related to Time



Clinical outcomes of 288 patients in the endovascular therapy group are given as modified Rankin Scale scores (range, 0-6, with lower scores indicating better outcomes) at 90 days stratified by time from the last known normal clinical status (LKN) to recanalization.

One strength of this study is the large multicenter balanced sample that has a concurrent medical management group. The study shows a direction of treatment effect consistent with those from the recently published RCTs.[1-5]

Conclusions

Despite inherent limitations of our retrospective design, our data suggest that EVT may be effective and safe for distal LVO (MCA M2 segment) relative to best medical management. A trial randomizing M2 segment occlusions to EVT vs medical management is warranted to determine the effectiveness of EVT, particularly in patients with disabling strokes despite occlusions in smaller-caliber vessels.

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Author Contributions: Dr Sarraj had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sarraj, Martin-Schild, Gupta.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Sarraj.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Bajgur.

Conflict of Interest Disclosures: Dr Sarraj reports serving as the lead principal investigator for the SELECT (Optimizing Patient's Selection For Endovascular Treatment in Acute Ischemic Stroke) trial, receiving an unrestricted grant from Stryker Neurovascular for the SELECT trial, and consulting for Stryker Neurovascular. Dr Vora reports consulting for Medtronic Neurovascular, Microvention Neurovascular, and Nanofiber Solutions. Dr Elijovich reports consulting for Siemens, Penumbra, Stryker, Covidien, and Microvention. Dr Abraham reports consulting for Stryker Neurovascular and serving on the speaker's bureau for Boehringer Ingelheim. Dr Janardhan reports serving as the principal investigator for the FIRST (A Clinical Trial to Assess the Acute Safety and Functional Outcome and Recovery After Stroke: The First Trial) study funded by Penumbra Inc, as a member of the data safety monitoring board for the Penumbra Pivotal Trial funded by Penumbra Inc, and as as a board member for Insera Therapeutics Inc and the Society of Vascular and Interventional Neurology. Dr Yoo reports receiving research grants for core imaging laboratory activities from Penumbra Inc and Neuravi Inc. Dr Sitton reports receiving grant support from the SELECT trial. Dr Gupta reports consulting to Stryker Neurovascular, Medtronic, and Rapid Medical, receiving royalties from UpToDate, and serving as an associate editor of the *Journal of Neurointerventional Surgery*, *Journal of Neuroimaging*, and *Interventional Neurology*. No other disclosures were reported.

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