ORIGINAL ARTICLE

Endovascular Treatment of Stroke Due to Medium-Vessel Occlusion

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ABSTRACT

BACKGROUND

Whether the large effect size of endovascular thrombectomy (EVT) for stroke due to large-vessel occlusion applies to stroke due to medium-vessel occlusion is unclear.

METHODS

In a multicenter, prospective, randomized, open-label trial with blinded outcome evaluation, we assigned patients with acute ischemic stroke due to medium-vessel occlusion who presented within 12 hours from the time that they were last known to be well and who had favorable baseline noninvasive brain imaging to receive EVT plus usual care or usual care alone. The primary outcome was the modified Rankin scale score (range, 0 [no symptoms] to 6 [death]) at 90 days, reported as the percentage of patients with a score of 0 or 1.

RESULTS

A total of 530 patients from five countries were enrolled between April 2022 and June 2024, with 255 patients assigned to the EVT group and 275 to the usual-care group. Most patients (84.7%) had primary occlusions in a middle-cerebral-artery branch. A modified Rankin scale score of 0 or 1 at 90 days occurred in 106 of 255 patients (41.6%) in the EVT group and in 118 of 274 (43.1%) in the usual-care group (adjusted rate ratio, 0.95; 95% confidence interval [CI], 0.79 to 1.15; P=0.61). Mortality at 90 days was 13.3% in the EVT group and 8.4% in the usual-care group (adjusted hazard ratio, 1.82; 95% CI, 1.06 to 3.12). Symptomatic intracranial hemorrhage occurred in 14 of 257 patients (5.4%) in the EVT group and in 6 of 272 (2.2%) in the usual-care group.

CONCLUSIONS

Endovascular treatment for acute ischemic stroke due to medium-vessel occlusion within 12 hours did not lead to better outcomes at 90 days than usual care. (Funded by the Canadian Institutes for Health Research and Medtronic; ESCAPE-MeVO ClinicalTrials.gov number, NCT05151172.)

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Acute ischemic stroke caused by an occlusion of the intracranial internal carotid artery or M1 segment (main trunk) of the middle cerebral artery (a large-vessel occlusion) causes high mortality, and outcomes without treatment are poor.[1] In contrast, acute ischemic stroke due to medium-vessel occlusion has a better prognosis because the point of occlusion in the vascular tree is located more distally and the volume of ischemic brain tissue downstream from the occlusion is smaller.[2] Nevertheless, half the patients with acute ischemic stroke due to a medium-vessel occlusion do not have an excellent outcome with currently available best medical care, and one third are not functionally independent 90 days after the index stroke.[3]

Pharmacologic treatment with an intravenous thrombolytic agent (e.g., alteplase or tenecteplase) is more likely to result in arterial recanalization of acute ischemic stroke due to medium-vessel occlusion than of stroke due to large-vessel occlusion. However, early recanalization after intravenous thrombolysis occurs less than 50% of the time.[4]

Endovascular thrombectomy (EVT) is a highly effective treatment for acute ischemic stroke due to large-vessel occlusion,[1,5] even among patients with extensive ischemic changes at baseline.[6] Data from post hoc analyses of randomized trials and nonrandomized studies suggest improvement in outcomes after EVT for acute ischemic stroke due to medium-vessel occlusion.[2,7] However, more-definitive data from prospective clinical trials specifically focused on the efficacy and safety of EVT for stroke due to medium-vessel occlusion are limited.[8,9] The Endovascular Treatment to Improve Outcomes for Medium Vessel Occlusions (ESCAPE-MeVO) trial was designed to evaluate whether EVT, in addition to usual care, would lead to good functional outcomes in patients with acute ischemic stroke caused by medium-vessel occlusion who presented within 12 hours from the time that they were last known to be well.

Methods

Trial Design

We conducted a phase 3, multicenter, prospective, randomized, open-label, controlled trial with blinded outcome evaluation (PROBE design).[10] Patients were assigned in a 1:1 ratio to receive EVT plus guideline-based usual care (EVT group) or guideline-based usual care alone (usual-care group). The trial was monitored by an independent data and safety monitoring committee. The trial funders were not involved in the design or conduct of the trial, the preparation or modification of the protocol or manuscript, or the collection and analysis of the data. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol,[10] available with the full text of this article at NEJM.org.

Participating sites were EVT-capable hospitals, and their ethics boards approved the trial. Patients or their legally authorized representative provided written informed consent, or emergency consent was obtained according to relevant local and national standards.

Randomization was performed with the use of a real-time, dynamic Web-based algorithm with minimal sufficient balance to achieve distribution balance with regard to patient age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score, arterial vascular territory (anterior vs. middle vs. posterior cerebral artery), and enrolling site.[11] The randomization time occurred after qualifying imaging was performed and was the time, recorded on the central server, when the enrolling physician or trial coordinator entered the key data variables for minimization into the Web-based system and then clicked on the randomization icon.

Patient Population

Eligible patients were adults recruited from hospital emergency departments at the time of presentation with an acute ischemic stroke caused by a medium-vessel occlusion. A medium-vessel occlusion was defined as an occlusion of the M2 or M3 segment of the middle cerebral artery, occlusion of the A2 or A3 segment of the anterior cerebral artery, or occlusion of the P2 or P3 segment of the posterior cerebral artery (Figs. S2 and S3 in the Supplementary Appendix, available at NEJM.org). The A1 and P1 segments were specifically not included.

Patients underwent randomization within 12 hours after stroke onset (defined as the time that the patient was last known to be well) and had to have a baseline NIHSS score greater than 5 (on a scale from 0 to 42, with higher scores indicating a more severe neurologic deficit) or a score of 3, 4, or 5 with a disabling deficit as judged by the treating medical team on the basis of occupation and life circumstance. Clinical

deficits were commensurate with the location of the occlusion, and evidence of salvageable brain tissue on baseline noninvasive imaging was required. Detailed inclusion and exclusion criteria are provided in the protocol.

Baseline neuroimaging followed local institutional workflows and protocols. Neuroimaging was performed either at the trial site (EVT-capable hospital) or, in case of interhospital transfer, at the peripheral hospital; imaging was repeated if deemed necessary by the treating medical team. Patients could qualify for the trial on the basis of computed tomography (CT) or magnetic resonance imaging (MRI) performed without the use of contrast material (lack of extensive ischemic changes on noncontrast CT or MRI of the head), CT angiography (CTA) or magnetic resonance angiography (MRA; presence of at least moderate collaterals on CTA or MRA), or perfusion imaging (visual evidence of core–penumbra mismatch on CT or magnetic resonance perfusion imaging). Detailed enrollment criteria regarding imaging are provided in the protocol.

TREATMENTS

Patients in the EVT group underwent EVT with the use of a Solitaire X family device (approved EVT device, Medtronic) for the first thrombus-retrieval attempt with or without concurrent aspiration. Additional endovascular-treatment attempts were conducted at the discretion of the operator with the use of any approved device or combination of devices. Guidance on rapid, effective, and safe EVT was provided and discussed with personnel at the trial sites. The use of general anesthesia was encouraged to enable safe navigation and deployment of endovascular devices in the distal arterial vasculature.

Patients in each trial group received current standard-of-care treatment as recommended by Canadian, U.S., and European guidelines[12-14] for the management of acute stroke. Treatment included intravenous thrombolysis with tenecteplase or alteplase if guideline-based indications for intravenous thrombolysis were met, stroke unit care, early rehabilitation, investigations for stroke mechanism, treatment for stroke prevention, and reduction of vascular risk.

CLINICAL ASSESSMENTS AND OUTCOMES

Patients' demographic characteristics, medical history, laboratory variables, and stroke symptoms and severity were assessed at presentation (see the protocol). The primary outcome was measured at 90 days on the modified Rankin scale, a 7-point ordered categorical scale with scores ranging from 0 (no disability) to 6 (death). The score was assessed by trained personnel who were unaware of the treatment assignment. Key secondary and safety outcomes included a modified Rankin scale score of 0, 1, or 2 at 90 days; mortality at 90 days; the Barthel Index score at 90 days; patient-reported quality of life; and infarct volume on 24-hour follow-up imaging.

Technical reperfusion success of EVT was assessed with the use of the Medium-Vessel Occlusion–Expanded Thrombolysis in Cerebral Infarction (MeVO-eTICI) score (range, 0 to 3, with higher scores indicating greater reperfusion).[2] Imaging assessment, including infarct-volume measurements, was performed by personnel at an independent central core laboratory who were unaware of patients' clinical data, including functional outcomes, and also unaware of treatment assignment when possible. Clinical data were validated by independent monitors.

STATISTICAL ANALYSIS

The statistical analysis of efficacy was conducted in the intention-to-treat population, which included all the patients according to the randomization assignment. The safety population included all the patients according to the treatment received (as-treated population), and the per-protocol population included all the patients who did not have a violation of an inclusion or exclusion criterion and received treatment according to the randomized assignment. The trial was powered to detect a shift in the distribution of modified Rankin scale scores at 90 days with scores of 5 and 6 collapsed into a single category, under an assumption that EVT would result in a common odds ratio (i.e., the odds of decrease of 1 point on the modified Rankin scale score) greater than 1.

A total sample of 500 patients was anticipated. The sample size was increased to 530 to account for potential loss to follow-up. One formal interim safety and efficacy analysis was performed on April 3, 2024, after 90-day follow-up was completed for 250 patients. The interim P value for success was defined according to the Lan–DeMets method of alpha spending, with a final P value for success of 0.0398. The outcome of the inter-

im analysis was simply the instruction to continue the trial to completion.

The primary outcome (modified Rankin scale score) was imputed with the use of the last-score-carried-forward approach if the score at day 30 was known and the patient was known to be alive at 90 days. If the scores at both day 30 and day 90 were missing and the patient was known to be alive at 90 days, the modified Rankin scale score was imputed to be 4 (see the Supplementary Appendix).

We report the data using standard descriptive statistics. We intended for the primary outcome to be analyzed with the use of a multivariable proportional-odds model, with adjustment for variables used in the minimization algorithm. However, the proportional-odds model was not better than a multinomial model on the basis of the Akaike information criterion, and the proportional-odds assumption was not statistically valid. This possibility was anticipated, and in accordance with the statistical analysis plan, we elevated the first secondary outcome — a modified Rankin scale score of 0 or 1 (indicating an excellent functional outcome), as compared with a score of 2 through 6, at 90 days — to the primary outcome. Unadjusted outcomes as a comparison of proportions with the use of Fisher's exact test and adjusted outcomes with the use of generalized linear modeling with a Poisson distribution and robust (Huber–White) variance esti-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	EVT + Usual Care (N=255)	Usual Care (N=274)
Age — yr		
Median	74	76
Interquartile range	63–82	65–83
Female sex — no. (%)	118 (46.3)	127 (46.4)
White race — no. (%)†	216 (84.7)	224 (81.8)
Medical history — no. (%)		
Hypertension	184 (72.2)	212 (77.4)
Hyperlipidemia	114 (44.7)	128 (46.7)
Ischemic heart disease	62 (24.3)	81 (29.6)
Diabetes mellitus	59 (23.1)	74 (27.0)
Previous stroke or transient ischemic attack	61 (23.9)	56 (20.4)
Smoking status — no. (%)		
Current smoker	31 (12.2)	49 (17.9)
Former smoker	66 (25.9)	73 (26.6)
Clinical presentation		
Atrial fibrillation or flutter on baseline electrocardiogram — no. (%)	81 (31.8)	76 (27.7)
NIHSS score‡		
Median	8	7
Interquartile range	6–11	5–11
Location of occlusion on CTA — no./total no. (%)§		
M2 segment of MCA, proximal	64/253 (25.3)	58/269 (21.6)
M2 segment of MCA, distal	63/253 (24.9)	41/269 (15.2)
M3 segment of MCA	90/253 (35.6)	126/269 (46.8)
ASPECTS¶		
Median	9	10
Interquartile range	8–10	9–10
Intravenous thrombolysis treatment — no. (%)	144 (56.5)	165 (60.2)

Table 1. (Continued.)

Characteristic	EVT + Usual Care (N = 255)	Usual Care (N = 274)
Time from onset to randomization — min‖		
Median	270	253
Interquartile range	160–438	148–396
Final MeVO-eTICI score of 2b, 2c, or 3 — no./total no. (%)**	190/253 (75.1)	—

* A full list of baseline characteristics is provided in Table S2. EVT denotes endovascular thrombectomy, and MCA middle cerebral artery.
† Race was reported by the patient.
‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating a more severe neurologic deficit.
§ The location of the occlusion at baseline was determined by means of CT angiography (CTA) in the majority of patients. Magnetic resonance angiography (MRA) was used in 3 patients (1 in the EVT group and 2 in the usual-care group). A total of 36 patients in the EVT group and 44 in the usual-care group had occlusions in the anterior or posterior cerebral artery. Core laboratory determinations were not available for 7 patients (2 in the EVT group and 5 in the usual-care group). The proximal M2 segment was defined as starting at the MCA main bifurcation or trifurcation (according to endovascular consensus statements[15,16]) and ending 1 cm distal to this point. The distal M2 segment followed thereafter and ended at the circular sulcus of the insula. The M3 segment was defined as the opercular segment.
¶ Values for the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) range from 0 to 10, with lower values indicating larger infarcts. The value was determined by the core laboratory.
‖ Angiographic interval times for three patients in the usual-care group who crossed over were as follows: the median time from door to arterial access, 100 minutes (interquartile range, 38 to 149); the median time from door to final reperfusion, 120 minutes (interquartile range, 50 to 208); and the time from onset to final reperfusion, 425 minutes (interquartile range, 290 to 468). The type of procedural sedation was general anesthesia in one patient, conscious sedation in one, and local anesthetic only in one. All three patients had an expanded Thrombolysis in Cerebral Ischemic score of 2b or 3 (on a scale of 0 to 3, with higher scores indicating more complete perfusion).
** The Medium Vessel Occlusion–expanded Thrombolysis in Cerebral Ischemic (MeVO-eTICI) reperfusion score ranges from 0 to 3, with higher scores indicating greater reperfusion.[2] A score of 2b, 2c, or 3 indicates successful reperfusion.

mates and log link were both used to generate rate ratios directly. Continuous variables were compared by means of a two-sample t-test, and then multiple linear regression was used to provide adjusted estimates of the effect size. Mortality was assessed with the use of a time-to-event analysis. Adjusted estimates of the risk of death were derived from a Cox proportional-hazards model. The proportional-hazards assumption was assessed both graphically and statistically and found to be valid.

All the secondary analyses, including the subgroup analysis of the primary treatment effect, were considered to be exploratory, and no adjustments for multiplicity were made. A P value of less than 0.05 was considered to indicate statistical significance, and all hypothesis tests were two-sided. Figures were drawn with Stata software, version 18.0 (StataCorp). Further details are provided in the statistical analysis plan, which was finalized before the database lock and is provided with the protocol.

RESULTS

PATIENTS

Between April 29, 2022, and June 28, 2024, a total of 530 patients were enrolled at 58 sites across five countries (Table S1). Patients were randomly assigned to receive either EVT plus usual care (255 patients) or usual care alone (275 patients) (Fig. S1). One patient who had been assigned to the usual-care group withdrew from the trial immediately after randomization and was not included in the intention-to-treat analyses. Among 44 patients (8.3%), there were 50 protocol violations (29 due to improper consent, 17 due to inclusion or exclusion criteria not being met, and 4 [in 0.8% of patients] due to treatment crossovers [3 from usual care to EVT and 1 from EVT to usual care]). An additional 8 patients in the EVT group did not have a Solitaire X device used first; thus, a total of 52 patients (9.8%) had protocol deviations. Primary-outcome data were missing and were imputed for 8 pa-

tients (3 in the EVT group and 5 in the usual-care group).

Overall, the characteristics of the patients at baseline were similar in the EVT group and the usual-care group (Table 1). The median age of the patients was 75 years (interquartile range, 64 to 82), and the numbers of men and women enrolled were nearly equal. The median baseline NIHSS score was 8 (interquartile range, 5 to 11), and the primary occlusion was in a middle-cerebral-artery branch in 84.7% of the patients. The representativeness of the patient population is shown in Table S3.

A majority of patients in each group were also treated with intravenous thrombolysis, either at a referring hospital or at the enrolling site. In the EVT group, the time from hospital arrival to arterial access was approximately 1.5 hours. Among 39 patients in the EVT group who had undergone recanalization at the time of the first angiographic imaging, 32 (82%) had received intravenous thrombolysis. EVT resulted in successful reperfusion (MeVO-eTICI score of 2b, 2c, or 3) in 75.1% of the patients. In the EVT group, the median time from onset to recanalization was 359 minutes, and 43.1% of the patients received general anesthesia.

Table 2. Efficacy Results.*

Outcome	EVT + Usual Care (N=255)	Usual Care (N=274)	Unadjusted Effect Size	Adjusted Effect Size
Primary outcome				
Modified Rankin scale score at 90 days†				
Median	2	2	—	—
Interquartile range	1–4	1–3		
Modified Rankin scale score of 0 or 1 at 90 days — no. (%)	106 (41.6)	118 (43.1)	Rate ratio, 0.97 (0.79 to 1.18)	Rate ratio, 0.95 (0.79 to 1.15)
Secondary outcomes				
Modified Rankin scale score of 0–2 at 90 days — no. (%)	138 (54.1)	161 (58.8)	Rate ratio, 0.92 (0.79 to 1.07)	Rate ratio, 0.92 (0.80 to 1.05)
Death at 90 days — no. (%)	34 (13.3)	23 (8.4)	Hazard ratio, 1.62 (0.95 to 2.75)	Hazard ratio, 1.82 (1.06 to 3.12)
Barthel Index ≥95 at 90 days — no./total no. (%)‡	130/243 (53.5)	167/258 (64.7)	Rate ratio, 0.83 (0.71 to 0.96)	Rate ratio, 0.81 (0.71 to 0.93)
EQ-5D-5L Index§	0.64±0.02	0.69±0.02	Difference, –0.04 (–0.11 to 0.02)	Beta coefficient, –0.05 (–0.11 to 0.01)
Mean EQ VAS score¶	61.8	63.4	Difference, –1.6 (–7.2 to 4.0)	Beta coefficient, –2.2 (–7.6 to 3.1)
Infarct volume — ml‖				
Mean volume at 18–54 hr	31.9	29.1	—	—
Volume with square-root transformation	4.35±0.23	4.30±0.20	Difference, –0.05 (–0.64 to 0.54)	Beta coefficient, 0.03 (–0.53 to 0.58)

* Plus–minus values are means ±SD except for the stroke volume, for which the square-root transformation is provided (see below).
† The primary outcome was the modified Rankin scale score at 90 days. Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. The primary outcome is reported as the percentage of patients with a modified Rankin scale score of 0 or 1 (indicating an excellent functional outcome).
‡ The Barthel Index is a categorical scale for basic activities of daily living with total scores ranging from 0 (cannot do any basic activities of daily living) to 100 (able to do all basic activities of daily living). Data were missing for 28 patients (5.3%; for 12 patients in the EVT group and for 16 in the usual-care group).
§ The EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Index ranges from 0 to 1, with a higher index indicating higher patient-reported quality of life. Data were missing for 69 patients (13.0%; for 34 patients in the EVT group and for 35 in the usual-care group).
¶ The EuroQol visual-analogue scale (EQ VAS) ranges from 0 to 100, with higher scores indicating higher patient-reported quality of life. Data were missing for 75 patients (14.2%; for 36 patients in the EVT group and for 39 in the usual-care group).
‖ Stroke volumes were nonnormally distributed, and so the standard deviation is not reported. The square-root transformation was closer to normal distribution and was used to provide the adjusted estimates. Four patients (0.8%; one in the EVT group and three in the usual-care group) had missing follow-up CT or MRI scans of the head. No imputation was done for these missing data.

EFFICACY OUTCOMES

The primary outcome (modified Rankin scale score at 90 days) was assessed at a median of 86 days after randomization. A modified Rankin scale score of 0 or 1, indicating an excellent functional outcome, occurred in 106 of 255 patients (41.6%) in the EVT group and in 118 of 274 patients (43.1%) in the usual-care group (adjusted rate ratio, 0.95, 95% confidence interval [CI], 0.79 to 1.15; P=0.61) (Table 2 and Fig. 1). A modified Rankin scale score of 0, 1, or 2 at 90 days occurred in 138 patients (54.1%) in the EVT group and in 161 patients (58.8%) in the usual-care group (adjusted rate ratio, 0.92; 95% CI, 0.80 to 1.05) (Table 2). Analysis of the treatment effect (modified Rankin scale score of 0 or 1) in prespecified subgroups suggested possible heterogeneity according to the time to treatment (Fig. S5).

The results for the secondary outcomes of the Barthel Index and patient-reported quality of life were similar to those for the primary outcome. Infarct volumes as measured on follow-up imaging of the head at 18 to 54 hours did not differ substantially between the two groups (31.9 ml in the EVT group and 29.1 ml in the usual-care group). Mortality appeared to be higher in the EVT group (13.3% [34 patients]) than in the usual-care group (8.4% [23 patients]) (adjusted hazard ratio, 1.82; 95% CI, 1.06 to 3.12) (Table 2 and Fig. S6). Results in both the per-protocol population and the as-treated population (Figs. S7 and S8) were similar to those in the intention-to-treat population.

SAFETY OUTCOMES

Safety was assessed in the as-treated population, which included 257 patients in the EVT group and 272 patients in the usual-care group. The incidence of serious adverse events was higher in the EVT group (33.9% [in 87 patients]) than in the usual-care group (25.7% [in 70 patients]) (Table 3). The most common of these events were pneumonia, recurrent stroke, progression or worsening of the index stroke, and symptomatic intracranial hemorrhage. Major procedural complications (e.g., vessel perforation or dissection) were rare and occurred in 5 patients in the EVT group. Only one procedural complication was considered by the investigators to be a serious adverse event. Symptomatic intracranial hemorrhage occurred in 14 patients (5.4%) in the EVT group and in 6 patients (2.2%) in the usual-care group (Table 3). Among these 20 patients, symptomatic hemorrhage was associated with death at 90 days in 12 (60%; in 7 patients in the EVT group and in 5 in the usual-care group).

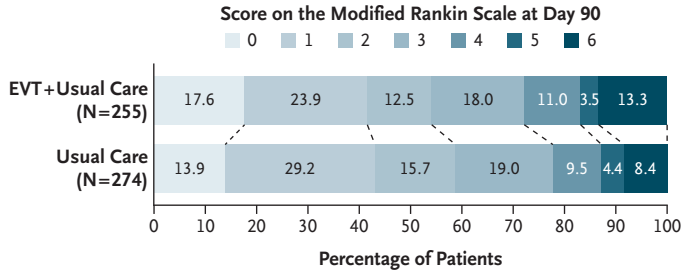

Figure 1. Distribution of Scores on the Modified Rankin Scale at 90 Days (Intention-to-Treat Population).

Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. The graph shows the distribution of scores at 90 days in the group that received endovascular thrombectomy (EVT) plus usual care and in the group that received usual care alone. The intention-to-treat population included all the patients who had undergone randomization, except for one patient who withdrew immediately after randomization. Percentages may not total 100 because of rounding.

DISCUSSION

In this randomized, open-label, phase 3 trial involving patients with acute ischemic stroke due to medium-vessel occlusion who presented within 12 hours from the time that they were last known to be well and who had evidence of salvageable tissue on baseline imaging, EVT did not lead to better functional outcomes at 90 days than usual care. No clear heterogeneity was observed among the prespecified subgroups, with the possible exception of the time from onset to randomization. We found that approximately 40% of the patients with stroke due to medium-vessel occlusion who received currently available best medical therapy had substantial disability at 90 days — a finding that supports results of previous cohort studies.[23,]

The ESCAPE-MeVO trial attempted to deliver rapid EVT to patients with acute, symptomatic medium-vessel occlusion who were selected on

Table 3. Serious Adverse Events and Intracranial Hemorrhage Classification (As-Treated Population).*

Variable	EVT + Usual Care (N=257)	Usual Care (N=272)
Any serious adverse event	87 (33.9)	70 (25.7)
Pneumonia	18 (7.0)	9 (3.3)
Recurrent stroke	14 (5.4)	10 (3.7)
Stroke progression	14 (5.4)	5 (1.8)
Symptomatic intracranial hemorrhage	14 (5.4)	6 (2.2)
Urinary tract infection	3 (1.2)	5 (1.8)
Covid-19	1 (0.4)	0
Other infection	7 (2.7)	4 (1.5)
New or worsening cancer	3 (1.2)	3 (1.1)
Seizure	3 (1.2)	5 (1.8)
Congestive heart failure	2 (0.8)	5 (1.8)
Endocarditis	2 (0.8)	1 (0.4)
Pulmonary embolus or deep venous thrombosis	2 (0.8)	3 (1.1)
Atrial fibrillation	1 (0.4)	5 (1.8)
Arterial-access complication	2 (0.8)	0
Procedural arterial injury	1 (0.4)	0
Heidelberg intracranial hemorrhage classification — no./total no. (%)†		
None	143/256 (55.9)	196/269 (72.9)
1a, Hemorrhagic infarction type 1	48/256 (18.8)	41/269 (15.2)
1b, Hemorrhagic infarction type 2	28/256 (10.9)	14/269 (5.2)
1c, Parenchymal hematoma type 1	13/256 (5.1)	11/269 (4.1)
2, Parenchymal hematoma type 2	4/256 (1.6)	4/269 (1.5)
3b, Intraventricular hemorrhage	1/256 (0.4)	1/269 (0.4)
3c, Subarachnoid hemorrhage	19/256 (7.4)	2/269 (0.7)

* The as-treated population included all the patients according to the treatment received. Serious adverse events were coded with the use of coding conventions from the *Medical Dictionary for Regulatory Activities*, version 20.0. Covid-19 denotes coronavirus disease 2019.

† Categories on the Heidelberg bleeding classification range from 1a to 3d.[17] Patients were classified into parenchymal hemorrhage categories 1 and 2 first; the 23 patients in categories 3b and 3c did not have any parenchymal hemorrhage. Among patients with parenchymal hemorrhage of any type, 32 patients had concurrent subarachnoid hemorrhage, 11 had concurrent intraventricular hemorrhage, and 3 had both subarachnoid and intraventricular hemorrhage. Classification was done by the core laboratory.

the basis of imaging. There are several possible reasons why EVT did not result in better outcomes than usual care. First, serious adverse events were more common in the EVT group than in the usual-care group. Although immediate procedural complications such as vessel injury were rare, some events, particularly symptomatic intracranial hemorrhage and stroke progression, may be attributable to the EVT procedure itself. Pneumonia and other infections could be related to adjunct interventions such as the type of procedural sedation. The summative effect could have resulted in the slightly higher mortality that was observed in the EVT group than in the usual-care group.

Second, technical EVT success could not be achieved in all cases, with approximately one quarter of the patients in the EVT group having an incomplete reperfusion pattern (final MeVO-eTICI score of 0 to 2a) on the last intracranial angio-

graphic imaging. Although there are technical differences between the MeVO-eTICI and eTICI scales, a trial of EVT for large-vessel occlusion resulted in reperfusion in 85% or more of the patients.[18]

Third, the workflow times in the ESCAPE-MeVO trial were longer than in previous trials that involved patients with large-vessel occlusion, with a median time from onset to recanalization of 359 minutes, as compared with 241 minutes in the ESCAPE trial.[19] It is possible that decision making in stroke due to medium-vessel occlusion is more nuanced than that in stroke due to large-vessel occlusion, and additional time may have been needed in some instances to arrange for general anesthesia. By comparison, general anesthesia was used in 9.1% of the patients in the ESCAPE trial and in 41.3% of those in the current trial.[20] Technical challenges in accessing the occluded vessel may have delayed reperfusion, particularly in smaller, distal occlusions. The implication is that EVT may have been performed too late, at a point at which the volume of salvageable tissue may not have been large enough to result in significantly better outcomes.

Fourth, a minority of patients (39 of 255 [15%]) with medium-vessel occlusion in the EVT group had undergone recanalization between qualifying noninvasive imaging and the time of the first intracranial angiographic imaging, and although the patients had angiography completed, a thrombectomy was not required. In a majority of those patients (32 of 39 [82%]), recanalization was associated with intravenous thrombolysis treatment.

The results of this trial differ from those of post hoc analyses of randomized trials and nonrandomized studies, the overwhelming majority of which have suggested that EVT is beneficial in stroke due to medium-vessel occlusion.[2,7] This discrepancy suggests that previous nonrandomized studies may have been subject to substantial selection bias and confounding — a situation that emphasizes the importance of rigorously conducted randomized, controlled trials.

We did not require trial sites to keep screening logs, and therefore we do not have information on how many patients presenting with stroke due to medium-vessel occlusion were ineligible for the trial on the basis of the exclusion criteria, nor do we know how many patients were treated with EVT outside the trial. It is possible that treatment of patients outside the trial biased the result toward the null. We did not attempt to credential individual neurointerventionalists within centers for the trial and instead focused on site selection using site-level metrics. This approach may have influenced both technical and safety outcomes. Finally, our trial mandated the first-line use of a Solitaire X device, and although the approach was procedurally safe, other technical approaches may be more effective.

The results of our trial do not support routine endovascular treatment of acute ischemic stroke due to medium-vessel occlusion. Further work is needed to improve the safety profile of the EVT procedure and to identify a population of patients who may benefit from this treatment approach.

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