ORIGINAL ARTICLE

Endovascular Treatment for Stroke Due to Occlusion of Medium or Distal Vessels

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ABSTRACT

BACKGROUND

Endovascular treatment (EVT) of stroke with large-vessel occlusion is known to be safe and effective. The effect of EVT for occlusion of medium or distal vessels is unclear.

METHODS

We randomly assigned participants with an isolated occlusion of medium or distal vessels (occlusion of the nondominant or codominant M2 segment of the middle cerebral artery [MCA]; the M3 or M4 segment of the MCA; the A1, A2, or A3 segment of the anterior cerebral artery; or the P1, P2, or P3 segment of the posterior cerebral artery) to receive EVT plus best medical treatment or best medical treatment alone within 24 hours after the participant was last seen to be well. The primary outcome was the level of disability at 90 days, as assessed with the modified Rankin scale score.

RESULTS

A total of 543 participants (women, 44%; median age, 77 years) were included in the analysis: 271 were assigned to receive EVT plus best medical treatment and 272 to receive best medical treatment alone. The median score on the National Institutes of Health Stroke Scale (range, 0 to 42, with higher scores indicating more severe symptoms) at admission was 6 (interquartile range, 5 to 9). Intravenous thrombolysis was given to 65.4% of the participants. The predominant occlusion locations were the M2 segment (in 44.0% of the participants), M3 segment (in 26.9%), P2 segment (in 13.4%), and P1 segment (in 5.5%). In the comparison between EVT plus best medical treatment and best medical treatment alone, no significant difference in the distribution of modified Rankin scale scores was observed at 90 days (common odds ratio for improvement in the score, 0.90; 95% confidence interval, 0.67 to 1.22; P=0.50). All-cause mortality was similar in the two groups (15.5% with EVT plus best medical treatment and 14.0% with best medical treatment alone), as was the incidence of symptomatic intracranial hemorrhage (5.9% and 2.6%, respectively).

CONCLUSIONS

In persons with stroke with occlusion of medium or distal vessels, EVT did not result in a lower level of disability or a lower incidence of death than best medical treatment alone. (Funded by the Swiss National Science Foundation and others; DISTAL ClinicalTrials.gov number, NCT05029414.)

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CME

Endovascular treatment (EVT) is beneficial in persons with an acute ischemic stroke caused by a large-vessel occlusion of the internal carotid artery, the M1 segment of the middle cerebral artery (MCA), or the basilar artery.[1-3] Evidence from randomized trials also suggests that EVT is beneficial in persons with acute occlusions of the dominant M2 segment of the MCA.[4] However, data from randomized, controlled trials are lacking on whether EVT is also beneficial in persons with occlusion of medium or distal vessels. Current American and European guidelines neither recommend nor discourage EVT in persons with occlusion of medium or distal vessels.[5,6] We therefore performed a randomized, controlled trial to assess whether EVT in addition to best medical treatment is more effective in reducing disability and death than best medical treatment alone in persons with an isolated occlusion of medium or distal vessels treated within 24 hours after the person was last seen to be well.

Methods

Trial Design and Oversight

The Endovascular Therapy plus Best Medical Treatment (BMT) versus BMT Alone for Medium Vessel Occlusion Stroke — A Pragmatic, International, Multicenter, Randomized Trial (DISTAL) was an investigator-initiated, international, assessor-blinded, randomized trial. It investigated whether EVT plus best medical treatment is superior to best medical treatment alone for reduction of disability and death in persons with an acute ischemic stroke due to an isolated occlusion of medium or distal vessels. The trial protocol (available with the full text in this article at NEJM.org) was approved by all responsible ethics committees and has been published previously.[7]

Written informed consent was obtained from all the participants or their legally authorized representatives either at the time of enrollment or post hoc (emergency consent procedures), according to country-specific requirements. The trial was conducted in accordance with the International Council for Harmonisation E6 guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki.

The trial was designed by the first two authors and the last author in consultation with the steering committee (see the Supplementary Appendix, available at NEJM.org), and data were gathered by the site investigators. The first two authors, a trial statistician, and the last author had full access to all the data in this trial. Data analysis was performed by a trial statistician. The steering committee and all the investigators vouch for the accuracy and completeness of the data, the fidelity of the trial to the protocol, and the accurate reporting of adverse events.

A Quick Take is available at NEJM.org

The trial was monitored by an independent data and safety monitoring board, and serious adverse events were adjudicated by an independent clinical events committee. Staff members of the Department of Clinical Research, University Hospital Basel, oversaw data management. Neuroimaging data were assessed by an independent core laboratory whose staff members were unaware of the clinical data. The legal sponsor of the trial was University Hospital Basel. The first draft of the manuscript was written by the first two authors and the last author. The decision to submit the manuscript for publication was made by the first and last authors and approved by all the coauthors. Funding bodies had no role in the design of the trial; the collection, monitoring, analysis, or interpretation of the data; or the writing of the manuscript.

Participants

Participants were eligible for inclusion if they were 18 years of age or older, lived at home before the stroke, had an acute ischemic stroke caused by an isolated occlusion of medium or distal vessels confirmed by means of computed tomographic (CT) angiography or magnetic resonance imaging (MRI) angiography, and had a National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating more severe symptoms) of at least 4. Lower NIHSS values at admission were allowed if symptoms were deemed to be disabling. On the basis of current evidence suggesting that EVT is beneficial for the treatment of dominant M2 occlusions, persons with these were excluded from the trial.[4] Occlusion of medium or distal vessels was defined as occlusion of the nondominant or codominant M2 segment of the MCA; the M3 or M4 segment of the MCA; the A1, A2, or A3 segment of the anterior cerebral artery; or the P1, P2, or P3 segment of the posterior cerebral artery. Participants could undergo randomization within 6 hours after they were last seen to be well or within 6 to 24 hours after they were last seen to be well provided that neuroimaging suggested

salvageable tissue. Detailed eligibility criteria are provided in Table S1 in the Supplementary Appendix and in the protocol.

TRIAL TREATMENT

Participants were randomly assigned in a 1:1 ratio with the use of a centralized Web-based system to receive EVT plus best medical treatment or best medical treatment alone. A probabilistic minimization method was used, with NIHSS score and trial site as stratification factors. The choice of EVT technique was left to the discretion of the treating physician. Any commercially available device was allowed. Trial participation had no effect on best medical treatment or aftercare.

Trial centers were experienced stroke centers in Europe and the Middle East and were selected in a two-step process by the first and last authors. All the participants were admitted to stroke units or intensive care units and treated according to current local or European guidelines (or both), including for thrombolysis.[8]

OUTCOMES

The primary outcome was the level of disability in performing daily activities at 90 days after the stroke as assessed with the modified Rankin scale[9]; scores range from 0 to 6, with higher scores indicating more severe disability. The modified Rankin scale score at 90 days was obtained during a clinical visit or in a structured telephone interview by an assessor who was unaware of the trial-group assignments. Investigators were required to be certified assessors of the modified Rankin scale.

Secondary efficacy outcomes were the change in severity of neurologic deficit (defined as the change from baseline in the normalized NIHSS score) at 24 hours and excellent functional outcome (modified Rankin scale score of 0 or 1), cognitive function, and health-related quality of life at 90 days. Safety outcomes included symptomatic intracranial hemorrhage according to the modified Safe Implementation of Thrombolysis in Stroke–Monitoring Study criteria within 24 hours (with a window of ±6 hours) after randomization[10] and death from any cause and all serious adverse events within 90 days after randomization.

In the participants assigned to receive EVT, reperfusion through the target vessel was assessed on the basis of the pre- and postprocedure angiography and adjudicated by the independent core laboratory. The modified Thrombolysis in Cerebral Infarction (TICI) scores were based on a comparison between the originally hypoperfused area (on baseline invasive angiography) and the postprocedural reperfusion, with grade 2b indicating reperfusion of 50 to 89% of the baseline affected territory, 2c indicating 90 to 99% reperfusion, and 3 indicating complete reperfusion (see the Supplementary Appendix).

STATISTICAL ANALYSIS

A priori power calculations indicated that 526 participants (with allowance for a 5% dropout rate) were needed to detect a 20% relative improvement in the modified Rankin scale score, with scores of 5 and 6 combined, with EVT at 80% power and a two-sided alpha of 0.05.[7] After approximately 263 participants (50%) had completed the 3-month follow-up period, an interim analysis for efficacy and futility was performed (see the Supplementary Appendix for details). The independent data and safety monitoring board recommended continuing the trial. The primary analysis used unadjusted mixed-effects ordinal regression, with a random intercept for center. Results are presented as common odds ratios for shifts toward better (i.e., lower) modified Rankin scale scores, with 95% confidence intervals. Analyses followed intention-to-treat principles on an imputed data set, with the use of multiple imputation by chained equations for missing data. An overview of the missing data is provided in Table S8.

Secondary outcomes were analyzed with the use of a serial gatekeeping strategy. After failure of gatekeeping, no further hypothesis testing was conducted, and results should be considered to be exploratory. For secondary outcomes and in subgroup analyses, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity and should not be used in place of a hypothesis test. Binary, ordinal, and continuous outcomes were assessed with the use of unadjusted mixed-effects logistic, ordinal, and linear or quantile (median) regression, respectively, with a random intercept for center. Supplementary analyses included predefined subgroup analyses and adjusted analyses. The evaluation

of model assumptions is described in the Supplementary Appendix. Safety outcomes were compared between groups with mixed-effects logistic regression adjusted for NIHSS score. All analyses were performed with R software (version 4.4.1). The full analysis plan is available with the protocol.

RESULTS

PARTICIPANTS

From December 2021 through July 2024, a total of 553 participants underwent randomization at 55 hospitals in 11 countries; almost all the participants were from European countries. Ten participants declined post hoc consent, leaving 543 participants (women, 44%; median age, 77 years) in the analysis: 271 were assigned to receive EVT plus best medical treatment and 272 to receive best medical treatment alone (Fig. 1, Table 1, and Table S3). The representativeness of the trial population is shown in Table S16. No participants were lost to follow-up, but 3 withdrew consent before completing the 3-month follow-up period.

The median NIHSS score at admission was 6 (interquartile range, 5 to 9), and 436 (80.3%) had a prestroke modified Rankin scale score of 0 or 1, 60 (11.0%) had a score of 2, and 45 (8.3%) had a score of 3 or 4 (data were missing for 2 participants). Before the stroke, 97.9% of the participants lived at home (513 of 524 participants; 19 had missing values). The median interval between the time that the participant was last seen to be well and randomization was 3.9 hours (interquartile range, 2.3 to 9.4), and 63.0% presented within 6 hours after the participant was last seen to be well. Predominant occlusion loca-

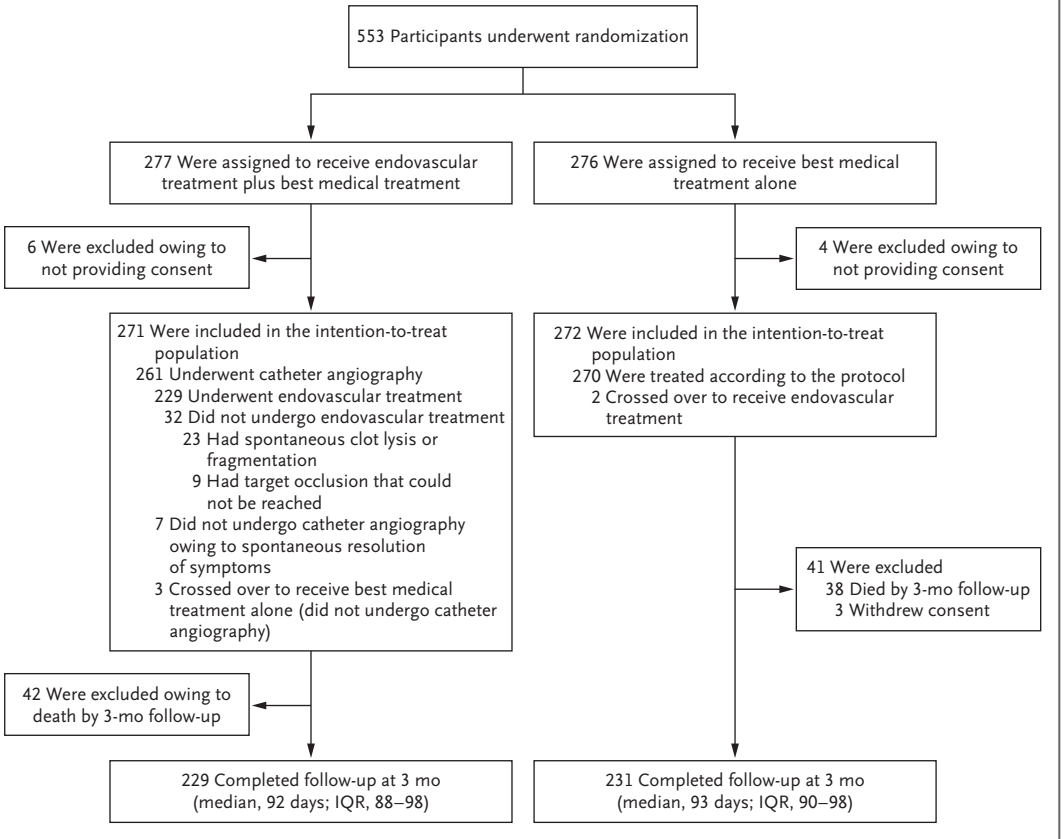

Figure 1. Randomization and Intention-to-Treat Analysis Population.

Participants were randomly assigned to receive endovascular treatment plus best medical treatment or best medical treatment alone. IQR denotes interquartile range.

Table 1. Baseline Characteristics of the Participants.*

Characteristic	EVT plus Best Medical Treatment (N=271)	Best Medical Treatment Alone (N=272)
Age		
Median (IQR) — yr	77 (68–83)	77.5 (68–84)
>80 yr — no. (%)	102 (37.6)	111 (40.8)
Female sex — no. (%)	116 (42.8)	123 (45.2)
Modified Rankin scale score before stroke — no./total no. (%)†		
0 or 1	223/271 (82.3)	213/270 (78.9)
2	28/271 (10.3)	32/270 (11.9)
3 or 4	20/271 (7.4)	25/270 (9.3)
Median NIHSS score at admission (IQR)‡	6 (5–9)	6 (5–9)
Occlusion location — no. (%)§		
M2 segment	129 (47.6)	110 (40.4)
M3 segment	62 (22.9)	84 (30.9)
M4 segment	3 (1.1)	0
A1 segment	0	1 (0.4)
A2 segment	11 (4.1)	5 (1.8)
A3 segment	9 (3.3)	5 (1.8)
P1 segment	17 (6.3)	13 (4.8)
P2 segment	32 (11.8)	41 (15.1)
P3 segment	6 (2.2)	11 (4.0)
No occlusion	1 (0.4)	2 (0.7)
M1 segment	1 (0.4)	0
Intravenous thrombolysis therapy — no. (%)	168 (62.0)	187 (68.8)
Interval between time that participant was last seen to be well and randomization (IQR) — hr	3.8 (2.3–9.0)	4.0 (2.3–9.9)
Interval between time that participant was last seen to be well and imaging (IQR) — hr	3.3 (1.6–8.8)	3.5 (1.6–9.5)
Interval between imaging and arterial puncture (IQR) — min	70.0 (54.0–95.0)	—
Interval between time that participant was last seen to be well and arterial puncture (IQR) — hr	4.9 (2.9–10.7)	—
Tandem occlusion — no. (%)¶	14 (5.2)	19 (7.0)

* Percentages may not total 100 because of rounding. EVT denotes endovascular treatment, and IQR interquartile range.
† Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating more severe disability.
‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe symptoms.
§ Occlusion locations were the M2 segment (mainly the eligible nondominant or codominant segment; exact percentages are shown in the Supplementary Appendix) of the middle cerebral artery (MCA); the M3 or M4 segment of the MCA; the A1, A2, or A3 segment of the anterior cerebral artery; and the P1, P2, or P3 segment of the posterior cerebral artery. One participant who was identified as having an M2 occlusion by the investigators at the trial site was rated as having an M1 occlusion by the independent core laboratory. In three participants, an occlusion was described by the investigators at the trial site but no occlusion was detected by the independent core laboratory.
¶ Tandem occlusion refers to a high-grade (>90%) extracranial stenosis or occlusion at the same location as the intracranial occlusion (or in the case of a posterior circulation occlusion of the extracranial vertebral artery).

tions on baseline imaging (CT or MRI angiography) were the M2 segment (44.0%) and the M3 segment (26.9%) of the MCA and the P2 segment (13.4%) and the P1 segment (5.5%) of the posterior cerebral artery. Intravenous thrombolysis was given to 65.4% of the participants.

INTERVENTION

EVT was performed in 229 of 271 participants (84.5%) assigned to receive EVT plus best medical treatment and in 2 of 272 (0.7%) assigned to receive best medical treatment alone (Fig. 1). The median interval between imaging and arterial puncture in participants assigned to receive EVT plus best medical treatment was 70 minutes (interquartile range, 54 to 95), and 71.7% had a final modified TICI score of 2b or better (indicating successful reperfusion) (Table S5), as compared with the capillary deficit on baseline digital subtraction angiography. The most used first-line EVT strategy was a primary combined approach (64.6%), whereas stent-retriever only and aspiration only were each used in 15.7% of the participants.

PRIMARY AND SECONDARY OUTCOMES

The results for the primary outcome are shown in Figure 2. There was no significant difference in the distribution of the modified Rankin scale scores between the participants assigned to receive EVT plus best medical treatment and those assigned to receive best medical treatment alone (unadjusted common odds ratio for improvement in the score, 0.90; 95% confidence interval [CI], 0.67 to 1.22, P=0.50). For all secondary outcomes, the treatment effect appeared to be neutral (Table 2).

SUBGROUP ANALYSIS

The results of the prespecified subgroup analyses are shown in Figure 3. There was not a substantial between-group difference in the distribution of modified Rankin scale scores in the prespecified subgroup of participants with a moderate-to-severe stroke as defined by an NIHSS score at admission of more than 5 (common odds ratio for improvement in the score, 1.02; 95% CI, 0.69 to 1.51). The results of other subgroup analyses were also consistent with those of the primary analysis.

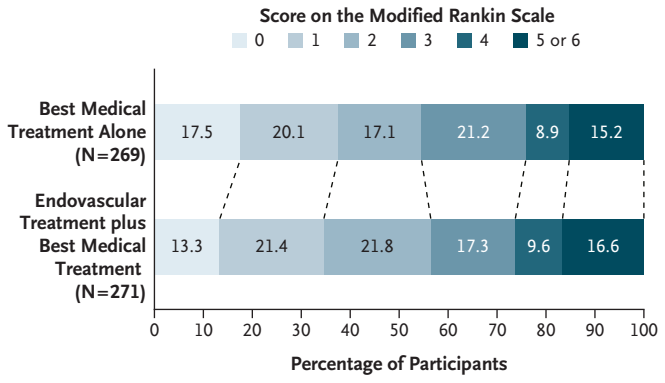

Figure 2. Modified Rankin Scale Scores at 90 Days.

Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating more severe disability.

SAFETY

The number of serious adverse events (114 in participants assigned to receive EVT plus best medical treatment and 88 in those assigned to receive best medical treatment alone; odds ratio, 1.27; 95% CI, 0.84 to 1.97) and of symptomatic intracranial hemorrhages (16 [5.9%] and 7 [2.6%], respectively; odds ratio, 2.38; 95% CI, 0.44 to 6.14) did not differ substantially between the two groups (Table 2). We observed no substantial difference in the incidence of death from any cause between participants assigned to receive EVT plus best medical treatment and those assigned to receive best medical treatment (15.5% and 14.0%, respectively; odds ratio, 1.17; 95% CI, 0.71 to 1.90).

DISCUSSION

The results of DISTAL, which involved a broad European population of persons with stroke with occlusion of medium or distal vessels treated under routine care conditions, show that EVT plus best medical treatment within 24 hours after symptom onset did not reduce disability or death at 90 days after randomization as compared with best medical treatment alone. The incidence of an excellent functional outcome was similar in the two groups. The prespecified safety variables (e.g., death, serious adverse events, and symptomatic intracranial hemorrhage) did not show substantial differences between the two groups.

Table 2. Outcomes According to Assigned Treatment.

Outcome	EVT plus Best Medical Treatment (N=271)	Best Medical Treatment Alone (N=272)	Treatment Effect (95% CI)*
Primary outcome			
Median modified Rankin scale score at 90 days (IQR)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	0.90 (0.67 to 1.22)†‡
Secondary clinical outcomes			
Excellent functional outcome at 90 days — no./total no. (%)§	94/271 (34.7)	101/269 (37.5)	0.88 (0.61 to 1.25)¶
Change in severity of neurologic deficit at 24 hr (IQR)‖	0.4 (–0.2 to 0.8)	0.3 (0.0 to 0.8)	0.02 (–0.10 to 0.14)**
Median quality-of-life scores (IQR)††			
Mobility	2.0 (1.0 to 3.0)	2.0 (1.0 to –3.0)	1.05 (0.74 to 1.49)†
Self-care	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)	1.25 (0.86 to 1.80)†
Everyday activities	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)	1.09 (0.76 to 1.55)†
Pain or physical discomfort	1.0 (1.0 to 2.0)	1.0 (1.0 to 3.0)	0.96 (0.66 to 1.40)†
Fear or depression	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)	1.13 (0.77 to 1.65)†
Visual analogue scale	70.0 (50.0 to 81.2)	70.0 (50.0 to 80.0)	0.94 (–3.59 to 5.74)**
Cognitive function‡‡	23.0 (18.2 to 26.0)	23.0 (18.0 to 27.0)	0.13 (–1.22 to 1.48) §§
Safety outcomes			
Death from any cause at 90 days — no. (%)	42 (15.5)	38 (14.0)	1.17 (0.71 to 1.90)¶¶
Symptomatic intracranial hemorrhage within 24 hr — no. (%)	16 (5.9)	7 (2.6)	2.38 (0.44 to 6.14)¶¶
Serious adverse events within 90 days — no.	114	88	1.27 (0.84 to 1.97)¶¶
Adverse event related to procedure or device — no. (%)			
Embolization in previously unaffected territory	17 (6.3)	—	
Arterial perforation	8 (3.0)	—	
Access hematoma	10 (3.7)	—	

* The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.
† The treatment effect represents the unadjusted common odds ratio (with its 95% confidence interval). Values higher than 1.0 indicate a shift toward a better outcome and those lower than 1.0 a shift toward a worse outcome.
‡ P=0.50.
§ An excellent functional outcome was defined as a modified Rankin scale score of 0 or 1.
¶ The treatment effect represents the unadjusted odds ratio (with its 95% confidence interval).
‖ The change in severity of neurologic deficit was defined as the change in the normalized NIHSS score.
** The treatment effect represents the unadjusted mean difference (with its 95% confidence interval).
†† The EuroQol Group 5-Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L) is a standardized instrument for the measurement of health status. The domains mobility, self-care, everyday activity, pain or physical discomfort, and fear or depression are assessed on a five-point scale, with 1 indicating no problem in this domain and 5 indicating extreme problems. The visual analogue scale ranges from 0 to 100, with 0 indicating the worst health imaginable and 100 the best health imaginable.
‡‡ Cognitive function was measured with the use of the Montreal Cognitive Assessment; scores range from 0 to 30, with higher scores indicating better cognitive ability.
§§ The treatment effect represents the unadjusted mean difference (with its 95% confidence interval).
¶¶ The treatment effect represents the adjusted odds ratio (with its 95% confidence interval), with adjustment for the stratification factor NIHSS score at admission.

Although the incidence of symptomatic intracranial hemorrhage was higher among participants assigned to receive EVT plus best medical treatment, this did not increase the percentage of participants who had severe disability or who died. Findings for secondary outcomes were in line with those of the primary analysis. Subgroup analyses suggest that the lack of superiority of EVT did not depend on baseline severity of neurologic deficit, time to treatment, occlusion location, or administration of intravenous thrombolysis.

Among participants assigned to receive EVT,

successful reperfusion was observed in 71.7%, a percentage below our initial projections but also below recently reported outcomes in trials of stroke with large-vessel occlusion.[11-13] This rather low incidence of successful reperfusion might have been a key contributor to the neutral finding of the trial. Because all participating sites were experienced in performing EVT, we believe that our trial represents actual practice. To achieve better outcomes in the interventional group, new techniques, devices, or both might need to be developed to treat these challenging occlusions. Despite best efforts to encourage fast delivery of EVT, the median interval between imaging and arterial puncture was 70 minutes, which was above the target of 60 minutes. This time delay might also have contributed to the decreased incidence of successful reperfusion, because trials involving patients with large-vessel occlusion have shown an association between faster treatment times and better reperfusion results.[14] A likely contributor to the longer interval between imaging and arterial puncture was a delay between imaging and randomization (median, 33.6 minutes), which can be attributed to the difficulties of detecting occlusion of medium or distal vessels and the

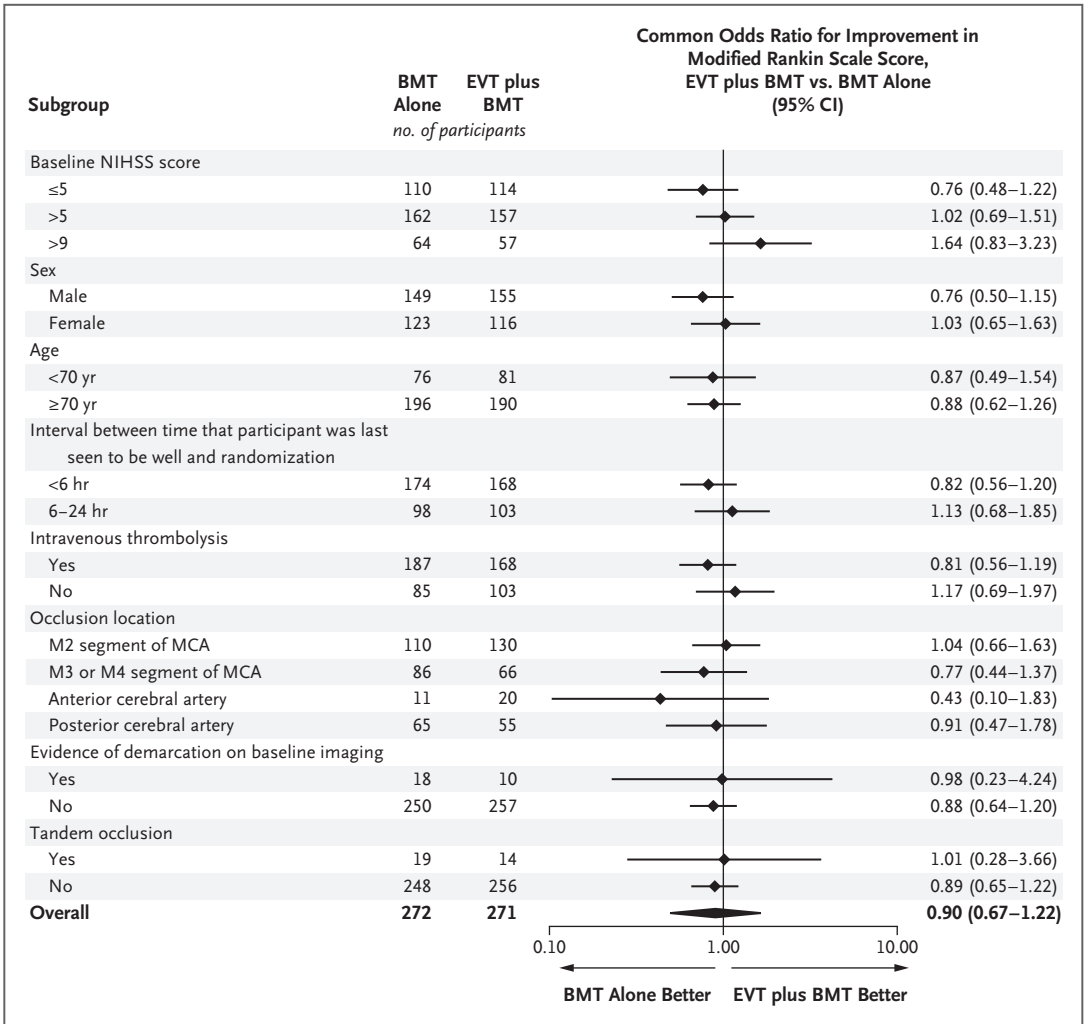

Figure 3. Subgroup Analyses.

The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe symptoms. BMT denotes best medical treatment, EVT endovascular treatment, and MCA middle cerebral artery.

time needed to acquire informed consent. It is possible that delays in treatment time that are attributable to trial procedures might have reduced the efficacy of EVT.[15] In addition, more distal arteries might be end arteries (without collateralization), which makes time to treatment potentially even more important for stroke with occlusion of medium or distal vessels because they have less capacity to compensate than stroke with large-vessel occlusions.

A strength of the trial design was the inclusion of persons with nondominant or codominant M2 occlusions and the exclusion of those with dominant M2 occlusions. This approach enabled us to estimate the efficacy of EVT in occlusion locations not previously included in randomized, controlled trials. Our trial does not confirm the assumption that occlusions of medium or distal vessels generally have a less severe clinical course. In both groups, only 55.2% of the participants had a favorable functional outcome (modified Rankin scale score of 0, 1, or 2), which is lower than previously reported[16] and which highlights the need for effective strategies to prevent disability and dependency. The percentage of patients assigned to receive best medical treatment alone who had a favorable functional outcome was in line with our initial projections based on data derived from the Swiss Stroke Registry.[7]

A potential limitation was the pragmatic trial design with its rather broad inclusion and exclusion criteria. Interventionalists could use their own judgment when selecting techniques and materials. However, this pragmatic approach provides a realistic assessment of the effects of EVT in the context of contemporary treatment and patient-selection practices. Another limitation is the treatment of occlusion of medium or distal vessels outside the trial: physicians' beliefs regarding the efficacy of EVT for occlusion of medium or distal vessels may have led to selective inclusion of participants. This interpretation is supported by the low baseline severity of some participants' stroke and the median age of the participants. However, we did not detect a signal for a treatment effect in the subgroups with an NIHSS score of more than 5 or age of younger than 70 years. Lastly, we observed a discrepancy between site and core-laboratory ratings of the location of the vessel occlusion; although sites used their best efforts to ensure enrollment of patients with nondominant or codominant M2 occlusions, the core laboratory rated a small proportion of M2 occlusions as dominant.

In a broad European population of persons with stroke with occlusion of medium or distal vessels, EVT plus best medical treatment did not result in a lower level of disability or a lower incidence of death than best medical treatment alone. Identification of persons who might benefit from EVT on the basis of imaging selection and potentially improved techniques or materials should be investigated in future randomized trials.

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REFERENCES

1. Jovin TG, Li C, Wu L, et al. Trial of thrombectomy 6 to 24 hours after stroke due to basilar-artery occlusion. N Engl J Med 2022;387:1373-84.

2. Tao C, Nogueira RG, Zhu Y, et al. Trial of endovascular treatment of acute basilar-artery occlusion. N Engl J Med 2022; 387:1361-72 .

3. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387: 1723-31.

4. Menon BK, Hill MD, Davalos A, et al. Efficacy of endovascular thrombectomy in patients with M2 segment middle cerebral artery occlusions: meta-analysis of data from the HERMES Collaboration. J Neurointerv Surg 2019;11:1065-9.

5. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50(12):e344-e418.

6. Turc G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO)–European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischaemic stroke endorsed by Stroke Alliance for Europe (SAFE). Eur Stroke J 2019; 4:6-12.

7. Marios-Nikos P, Alex B, Jens F, et al. EnDovascular therapy plus best medical treatment (BMT) versus BMT alone for medIum distal veSsel occlusion sTroke (DISTAL): an international, multicentre, randomized-controlled, two-arm, assessor-blinded trial. Eur Stroke J 2024;9:1083-92.

8. Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute

ischaemic stroke. Eur Stroke J 2021;6(1):I-LXII.
9. Saver JL, Chaisinanunkul N, Campbell BCV, et al. Standardized nomenclature for modified Rankin scale global disability outcomes: consensus recommendations from Stroke Therapy Academic Industry Roundtable XI. Stroke 2021;52:3054-62.
10. Mazya M, Egido JA, Ford GA, et al. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: Safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. Stroke 2012;43:1524-31.
11. Costalat V, Jovin TG, Albucher JF, et al. Trial of thrombectomy for stroke with a large infarct of unrestricted size. N Engl J Med 2024;390:1677-89.
12. Sarraj A, Hassan AE, Abraham MG, et al. Trial of endovascular thrombectomy for large ischemic strokes. N Engl J Med 2023;388:1259-71.
13. Fischer U, Kaesmacher J, Strbian D, et al. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. Lancet 2022;400:104-15.
14. Bourcier R, Goyal M, Liebeskind DS, et al. Association of time from stroke onset to groin puncture with quality of reperfusion after mechanical thrombectomy: a meta-analysis of individual patient data from 7 randomized clinical trials. JAMA Neurol 2019;76:405-11.
15. Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA 2016;316:1279-88.
16. Ospel JM, Menon BK, Demchuk AM, et al. Clinical course of acute ischemic stroke due to medium vessel occlusion with and without intravenous alteplase treatment. Stroke 2020;51:3232-40.