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A Randomized Trial of Intravenous Alteplase before Endovascular Treatment for Stroke

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ABSTRACT

BACKGROUND

The value of administering intravenous alteplase before endovascular treatment (EVT) for acute ischemic stroke has not been studied extensively, particularly in non-Asian populations.

METHODS

We performed an open-label, multicenter, randomized trial in Europe involving patients with stroke who presented directly to a hospital that was capable of providing EVT and who were eligible for intravenous alteplase and EVT. Patients were randomly assigned in a 1:1 ratio to receive EVT alone or intravenous alteplase followed by EVT (the standard of care). The primary end point was functional outcome on the modified Rankin scale (range, 0 [no disability] to 6 [death]) at 90 days. We assessed the superiority of EVT alone over alteplase plus EVT, as well as noninferiority by a margin of 0.8 for the lower boundary of the 95% confidence interval for the odds ratio of the two trial groups. Death from any cause and symptomatic intracerebral hemorrhage were the main safety end points.

RESULTS

The analysis included 539 patients. The median score on the modified Rankin scale at 90 days was 3 (interquartile range, 2 to 5) with EVT alone and 2 (interquartile range, 2 to 5) with alteplase plus EVT. The adjusted common odds ratio was 0.84 (95% confidence interval [CI], 0.62 to 1.15; P=0.28), which showed neither superiority nor noninferiority of EVT alone. Mortality was 20.5% with EVT alone and 15.8% with alteplase plus EVT (adjusted odds ratio, 1.39; 95% CI, 0.84 to 2.30). Symptomatic intracerebral hemorrhage occurred in 5.9% and 5.3% of the patients in the respective groups (adjusted odds ratio, 1.30; 95% CI, 0.60 to 2.81).

CONCLUSIONS

In a randomized trial involving European patients, EVT alone was neither superior nor noninferior to intravenous alteplase followed by EVT with regard to disability outcome at 90 days after stroke. The incidence of symptomatic intracerebral hemorrhage was similar in the two groups. (Funded by the Collaboration for New Treatments of Acute Stroke consortium and others; MR CLEAN NO IV ISRCTN number, ISRCTN80619088.)

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*A full list of the MR CLEAN NO IV investigators is provided in the Supplementary Appendix, available at NEJM.org.

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In areas where endovascular treatment (EVT) is available, the procedure has become the standard of care for patients with acute ischemic stroke due to intracranial large-vessel occlusion in the anterior circulation.[1,2] Because EVT was shown to provide benefit when given in addition to best medical management, including intravenous alteplase, guidelines recommend administration of alteplase before EVT in eligible patients.[2,3] Intravenous alteplase may increase the incidence of early reperfusion or lyse distal emboli after thrombectomy.[4-6] However, alteplase alone infrequently recanalizes large-vessel occlusions before EVT and has been associated with an increased risk of intracerebral hemorrhage.[5,7,8]

Two trials in China showed that EVT alone was noninferior to alteplase followed by EVT.[9,10] A smaller trial in Japan showed similar disability outcomes with EVT alone and EVT combined with treatment with a lower alteplase dose than that used in the Chinese trials but did not show noninferiority of EVT alone.[11] A study-level meta-analysis of these trials showed similar outcomes for the two treatment strategies.[12] Differences in populations, stroke types, and health care organizations may explain these disparate findings and limit generalizability of these results to non-Asian countries.[13,14] The aim of our trial, MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) NO IV, was to determine whether EVT alone would be more effective, or noninferior, as compared with intravenous alteplase followed by EVT in European patients with acute ischemic stroke due to an intracranial anterior-circulation stroke who present to EVT-capable centers.

Methods

Trial Design

This was an investigator-initiated, international, multicenter, prospective, randomized, open-label trial with blinded end-point assessment. The trial protocol was approved by the Dutch, Belgian, and French central ethical committees and by research boards at each participating center. The final versions of the trial protocol and statistical analysis plan (both available with the full text of this article at NEJM.org) were completed on July 15 and November 18, 2020, respectively.[15] Final patient enrollment and database closure were on October 28, 2020, and February 5, 2021, respectively. The trial was conducted in accordance with the revised Helsinki guidelines.

The trial was funded by the Collaboration for New Treatments of Acute Stroke consortium, which is funded by the Netherlands Cardiovascular Research Initiative (an initiative of the Dutch Heart Foundation), the Brain Foundation Netherlands, Medtronic, Cerenovus, and Stryker. There was no commercial involvement in the design or planning of the trial or in the analysis or reporting of the data by any of the parties providing funding. The trial used a deferred-consent procedure in accordance with national legislation in the participating countries.[16] Patients or their legal representatives were asked to provide written informed consent as soon as possible after treatment. Patient eligibility was assessed by the treating physician. Members of the executive and steering committees designed the trial and protocol, collected the data, met monthly to oversee the trial, and wrote the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Patients and Centers

The trial was carried out in 20 hospitals in the Netherlands, Belgium, and France (listed in Table S1 in the Supplementary Appendix, available at NEJM.org). Patients were 18 years of age or older, had acute ischemic stroke due to an intracranial proximal occlusion of the anterior circulation, were eligible for EVT and intravenous alteplase administration within 4.5 hours after symptom onset according to local guidelines, and were admitted directly to a center that performed EVT.[2,3,17] Symptom onset was defined as the witnessed time of onset of stroke-related neurologic symptoms or the time at which the patient was last seen well. Patients were eligible if they had a score of 2 or more on the National Institutes of Health Stroke Scale (NIHSS; range, 0 [no symptoms] to 42 [most severe deficits]). Proximal anterior-circulation occlusion was defined as occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery (M1), or the proximal second segment of the middle cerebral artery (M2), as as-

sessed by computed tomographic angiography (CTA) or magnetic resonance angiography (MRA). The protocol allowed active lowering of blood pressure to facilitate the safe administration of alteplase. Detailed inclusion criteria are provided in the trial protocol. We did not keep an eligibility screening log.

TRIAL PROCEDURES

Patients were randomly assigned in a 1:1 ratio to receive either EVT alone or intravenous alteplase followed by EVT (usual care). Randomization was performed by means of a Web-based system with the use of permuted blocks stratified according to center and whether they were included in the Multicenter Randomized Trial of Acute Stroke Treatment in the Ambulance with a Nitroglycerin Patch.[15,18] That trial investigated treatment with a nitroglycerin patch in the ambulance for patients with suspected stroke (see the Methods section in the Supplementary Appendix); only nine patients were included in both trials (Table S2). Patients, local investigators, and treating physicians were aware of the trial-group assignments.

Patients who were assigned to the usual-care group received intravenous alteplase before EVT (0.9 mg per kilogram of body weight [maximum, 90 mg]; 10% as bolus and 90% as 1-hour infusion), and the initiation of EVT before the end of alteplase infusion was permitted, as advised in current guidelines.[2,3] Patients in the EVT-alone group underwent EVT without preceding alteplase administration. Rescue intravenous alteplase (0.9 mg per kilogram) was permitted in the EVT-alone group if there was incomplete reperfusion after EVT (defined as a score of 0, 1, or 2A on the extended Thrombolysis in Cerebral Infarction [eTICI] scale; range, 0 [no reperfusion] to 3 [complete reperfusion]) within 4.5 hours after stroke onset. EVT was performed with any Conformit Europ enne approved stent retriever. Suction catheters (Conformit Europ enne approved) were allowed as a rescue approach after these devices came into common use. Intraarterial application of alteplase was permitted at the discretion of the interventionist (maximum dose, 30 mg).

Primary end-point data were collected through standardized telephone interviews (see the Methods section in the Supplementary Appendix) by trained research nurses who were unaware of the trial-group assignments.[19,20] Independent committees, whose members were unaware of the trial-group assignments, adjudicated serious-adverse-event reports and primary end-point data on the basis of the interview reports. Imaging was assessed with standardized case-report forms by an imaging committee whose members were unaware of clinical data except for the side of the body with stroke symptoms. An independent data monitoring board monitored safety and performed prespecified efficacy analyses after inclusion of the 100th, 250th, and 400th enrolled patient; the board used a Haybittle Peto stopping boundary and determined at each analysis that the trial should continue.[15] Investigators were unaware of the results of the interim analyses.

TRIAL END POINTS

The primary end point was functional outcome on the modified Rankin scale (range, 0 [no disability] to 6 [death]) at 90 days (±14 days) after randomization, analyzed for superiority and then for noninferiority.[21] There were eight secondary end points: recanalization on the first intracranial angiogram (absence of treatable occlusion by the time of EVT); successful reperfusion on the final intracranial angiogram (eTICI score of 2B, 2C, or 3); recanalization on CTA or MRA at 24 hours (modified Arterial Occlusive Lesion score of 2 to 3, with scores ranging from 0 [no recanalization] to 3 [complete recanalization]); the NIHSS score at 24 hours and at 5 to 7 days or discharge (if earlier); the final lesion volume on magnetic resonance imaging (MRI) at 24 hours or on noncontrast computed tomography (CT) at 5 or 7 days or at discharge (see the Methods section in the Supplementary Appendix); a comparison within three dichotomized groups with respect to the score on the modified Rankin scale (0 or 1 vs. 2 to 6, 0 to 2 vs. 3 to 6, and 0 to 3 vs. 4 to 6) at 90 days; the score on the EuroQol Group 5-Dimension 5-Level Self-Report questionnaire (EQ-5D-5L; range, −0.446 to 1.00, with higher scores indicating better quality of life)[22] at 90 days; and the score on the Barthel Index[23] (dichotomized as 0 to 94 vs. 95 to 100, with 95 to 100 indicating no interference with daily activities) at 90 days. Safety end points were any intracranial hemorrhage and symptomatic intracerebral hemorrhage according to the Heidelberg

Bleeding Classification,[24] postprocedure femoral-artery aneurysm or groin hematoma, embolization to new cerebral territory, infarction in new cerebral vascular territory on noncontrast CT at 5 to 7 days or discharge or on diffusion-weighted MRI at 24 hours, and death from any cause within 90 days.

STATISTICAL ANALYSIS

The statistical analysis plan was published previously with the trial protocol.[15] Sample-size calculations used the distribution of scores on the modified Rankin scale in the intervention group of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands as a reference.[25] We assumed a treatment effect with a common odds ratio of 1.54, corresponding to an absolute difference of approximately 8 percentage points between the trial groups in the percentage of patients with a score on the modified Rankin scale of 0 to 2, and we used Monte Carlo simulations with 5000 runs. After covariate adjustment, a sample of 540 patients would provide 91% power to detect a true treatment effect with a two-sided alpha level of 0.05. We specified a noninferiority margin with a lower boundary of the 95% confidence interval of the common odds ratio of 0.8. With the use of a two-sided confidence interval, a noninferiority boundary of 0.8 constitutes 97.5% certainty that EVT alone does not differ more than approximately 5 percentage points in the percentage of patients with a modified Rankin score of 0 to 2 in favor of standard treatment.[26]

The primary analysis assessed the superiority of EVT alone over alteplase with EVT according to the assigned trial group in the modified intention-to-treat population, which consisted of all the patients who provided consent, followed by assessment of noninferiority of EVT alone. Secondary and safety end points were compared between the trial groups. We performed sensitivity analyses in the as-treated population; details are provided in the statistical analysis plan.

The primary effect was determined by the common odds ratio, with a 95% confidence interval, for a shift in the direction of better outcome on the modified Rankin scale; this ratio was estimated with ordinal logistic regression. Assessment of proportionality by the Harrell graphical method did not show visually significant departures from proportional odds.[27] Binary logistic regression was used for dichotomous end points to estimate odds ratios. Continuous endpoint data were log transformed if necessary, to satisfy assumptions for linear regression, resulting in beta coefficients with 95% confidence intervals. The primary and secondary analyses were adjusted for age, baseline NIHSS score, collateral status, prestroke score on the modified Rankin scale, and time from symptom onset to randomization.[15] Treatment effect was assessed in prespecified subgroups defined according to age, baseline NIHSS score, time from symptom onset to randomization (all by thirds), occlusion location (terminal internal carotid artery, M1, or M2), internal carotid artery tandem lesion (intracranial occlusion combined with flow-limiting cervical internal carotid artery lesion), collateral status, and atrial fibrillation with multiplicative interaction terms. For secondary analyses, there was no prespecified plan for adjustment of confidence intervals for multiplicity, and no definite inferences can be drawn from these data.

For regression analyses, missing data were imputed with the use of multiple-imputation methods, except that patients who died during the trial period received the worst score for all missing clinical outcomes. No alpha was expended as a result of interim analyses. All analyses were performed by an independent statistician using R software, version 4.0.3 (R Foundation for Statistical Computing, www.r-project.org).

RESULTS

PATIENTS

From January 24, 2018, to October 28, 2020, a total of 547 patients underwent randomization. There were no screening logs to determine the number of patients who were eligible for enrollment and may have been treated outside the trial. Of the 547 patients, 539 provided deferred consent for participation and were included in the modified intention-to-treat analysis (Fig. 1 and Fig. S1); 273 patients were assigned to receive EVT alone and 266 to receive intravenous alteplase followed by EVT. No patients were lost to follow-up, but data for the main covariates were missing for 7 patients (Table 1).

The demographic and clinical characteristics of the patients at baseline were similar in the two trial groups, except for a higher percentage of patients with atrial fibrillation or terminal

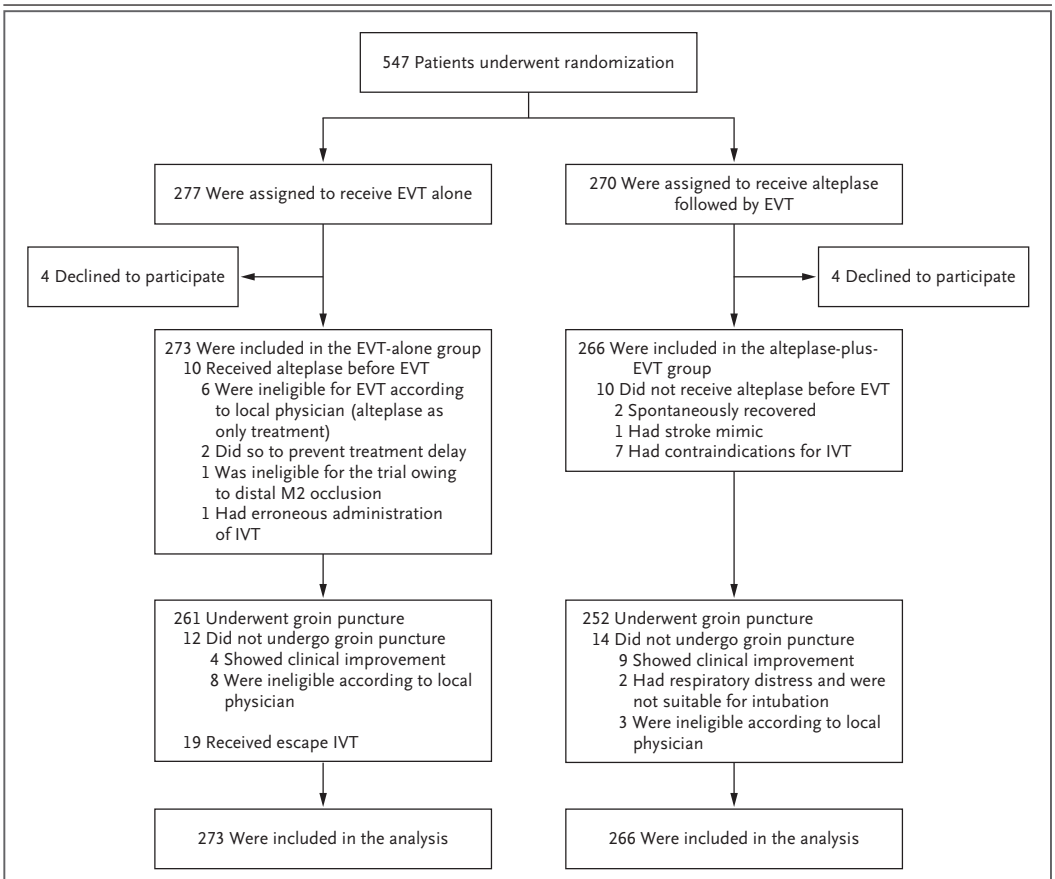

Figure 1. Randomization, Inclusion, and Treatment of Patients.

In a 1:1 ratio, patients were randomly assigned to receive either endovascular treatment (EVT) alone or intravenous alteplase followed by EVT (usual care). Owing to deferral of consent, 8 patients underwent randomization but were not included after they declined to participate. One patient withdrew consent after trial enrollment was closed, which led to a total sample of 539 rather than 540 patients. All the patients who received EVT underwent groin puncture initially; in 3 patients in the EVT-alone group and 1 patient in the alteplase-plus-EVT group, direct carotid puncture was performed because intracranial catheterization through the aorta was not possible. Additional information is provided in Figure S1 in the Supplementary Appendix. IVT denotes intravenous thrombolysis with alteplase, and M2 the second segment of the middle cerebral artery.

internal carotid artery occlusions and a slightly higher age in the EVT-alone group (Table 1 and Table S2). Overall, the median age of the patients was 71 years (interquartile range, 61 to 79), and 56.6% were men. The median time from stroke onset to alteplase administration in the usual-care group was 98 minutes (interquartile range, 75 to 156). Of the 273 patients assigned to receive EVT alone, 10 (3.7%) received intravenous alteplase before EVT (Fig. 1 and Table S3); 19 of 261 patients with available data (7.3%) received rescue intravenous alteplase (Table S4). In total, 26 of 539 patients (4.8%) did not undergo groin puncture (Fig. 1 and Table S5). Aspiration was used as the first-line EVT approach in 54 of 247 patients (21.9%) in the EVT-alone group and 48 of 229 patients (21.0%) in the alteplase-plus-EVT group.

PRIMARY END POINT

The median score on the modified Rankin scale at 90 days was 3 (interquartile range, 2 to 5) in the EVT-alone group and 2 (interquartile range, 2 to 5) in the alteplase-plus-EVT group; the adjusted odds ratio for a shift in the score on the modified Rankin scale at 90 days comparing

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

Characteristic	EVT Alone (N=273)	Alteplase Followed by EVT (N=266)
Median age (IQR) yr	72 (62 80)	69 (61 77)
Male sex no. (%)	161 (59.0)	144 (54.1)
Median NIHSS score (IQR)	16 (10 20)	16 (10 20)
Medical history		
Ischemic stroke no. (%)	47 (17.2)	44 (16.5)
Atrial fibrillation no. (%)	86 (31.5)	63 (23.7)
Diabetes mellitus no. (%)	40 (14.7)	50 (18.8)
Hypertension no./total no. (%)	121/273 (44.3)	139/265 (52.5)
Prestroke score on the modified Rankin scale no./total no. (%)		
0	189/272 (69.5)	185/266 (69.5)
1	51/272 (18.8)	49/266 (18.4)
2	24/272 (8.8)	25/266 (9.4)
≥3	8/272 (2.9)	7/266 (2.6)
Median systolic blood pressure (IQR) mm Hg	150 (135 167)	150 (130 169)
Median glucose level (IQR) mmol/liter	6.6 (5.8 7.6)	6.8 (5.9 8.5)
Median ASPECTS (IQR)‖	9 (8 10)	9 (8 10)
Location of intracranial occlusion no./total no. (%)**		
Intracranial ICA	4/272 (1.5)	0/266
Terminal ICA	64/272 (23.5)	50/266 (18.8)
M1	156/272 (57.4)	174/266 (65.4)
Proximal M2	45/272 (16.5)	40/266 (15.0)
None	3/272 (1.1)	2/266 (0.8)
Tandem lesion no./total no. (%)	48/257 (18.7)	40/250 (16.0)
Collateral score no./total no. (%)		
0	20/267 (7.5)	12/259 (4.6)
1	73/267 (27.3)	79/259 (30.5)
2	112/267 (41.9)	111/259 (42.9)
3	62/267 (23.2)	57/259 (22.0)
Median duration (IQR) min		
From stroke onset to randomization	94 (69 137)	93 (71 152)
From stroke onset to start of alteplase	NA	98 (75 156)
From stroke onset to groin puncture	130 (103 180)	135 (106 185)
From door to needle	NA	31 (24 44)
From needle to groin puncture‖‖	NA	28 (20 41)
From door to groin puncture	63 (50 78)	64 (51 78)

* Percentages may not total 100 because of rounding. EVT denotes endovascular treatment, ICA internal carotid artery, IQR interquartile range, M1 first segment of the middle cerebral artery, M2 second segment of the middle cerebral artery, and NA not applicable.

Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating a more severe neurologic deficit. Two patients had a pure sensory stroke that was considered to be clinically disabling.

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

Data were missing for 1 patient in the EVT-alone group and 2 patients in the alteplase-plus-EVT group.

Table 1. (Continued.)

Data were missing for 4 patients in the EVT-alone group and 3 patients in the alteplase-plus-EVT group.
‖ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) quantifies early ischemic changes in the brain on computed tomography (CT). A score of 10 indicates no changes, and 1 point is subtracted for each affected brain region.
** The location of the intracranial occlusion was scored by the core laboratory. Five patients had an isolated occlusion of the extracranial ICA and thus were scored as having no intracranial occlusion. For 1 patient in the EVT-alone group, the occlusion location on CT angiography could not be assessed owing to motion artifacts.
Tandem lesion was defined as an intracranial target occlusion with ipsilateral extracranial carotid dissection, clinically significant atherosclerotic stenosis, or atherosclerotic occlusion.
The collateral score quantifies the extent of collateral flow visible on CT angiography. The score ranges from 0, indicating no collaterals, to 3, indicating collateral flow to 100% of the affected territory.
Data were missing for 15 patients.
Data were missing for 12 patients in the EVT-alone group and 28 in the alteplase-plus-EVT group.
‖‖ Data were missing for 28 patients.

EVT alone with alteplase plus EVT was 0.84 (95% confidence interval [CI], 0.62 to 1.15; P=0.28) (Fig. 2 and Table 2). These findings indicate that EVT alone was not superior to alteplase followed by EVT and was not noninferior, because the lower boundary of the 95% confidence interval included 0.8. The as-treated sensitivity analysis yielded similar results (adjusted odds ratio, 0.84; 95% CI, 0.61 to 1.16) (Table S7).

SECONDARY END POINTS

The incidence of recanalization on the first angiogram (preceding EVT) was similar in the two trial groups (2.8% with EVT alone and 3.7% with alteplase plus EVT; adjusted odds ratio, 0.79; 95% CI, 0.42 to 1.47) (Table 2). Successful reperfusion occurred in 192 of 244 patients (78.7%) in the EVT-alone group and in 196 of 236 (83.1%) in the alteplase-plus-EVT group (adjusted odds ratio, 0.73; 95% CI, 0.47 to 1.13). Recanalization on follow-up imaging occurred in 78.2% in the EVT-alone group and in 84.7% in the alteplase-plus-EVT group (adjusted odds ratio, 0.82; 95% CI, 0.52 to 1.28). The median NIHSS score at 5 to 7 days or discharge was 4 in the EVT-alone group and 3 in the alteplase-plus-EVT group (adjusted beta coefficient, 0.21; 95% CI, 0.03 to 0.38). The follow-up lesion volume

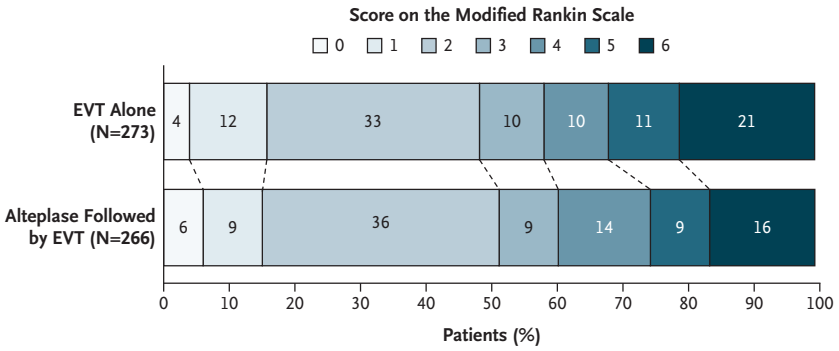

Figure 2. Distribution of Scores on the Modified Rankin Scale at 90 Days in the Modified Intention-to-Treat Population.

Shown are the scores on the modified Rankin scale of all included patients with available 90-day follow-up data. The modified intention-to-treat population included all the patients who provided consent, and patients were included in the analysis according to their assigned trial group. Scores range from 0 to 6, with 0 indicating no symptoms or disability after stroke, 1 no clinically relevant disability, 2 slight disability, 3 moderate disability, 4 moderate-to-severe disability, 5 severe disability (complete dependence on daily care), and 6 death. EVT alone was neither superior nor noninferior to intravenous alteplase followed by EVT, also after adjustment for age, baseline National Institutes of Health Stroke Scale score, collateral status, prestroke score on the modified Rankin scale, and time from symptom onset to randomization (adjusted common odds ratio, 0.84; 95% confidence interval, 0.62 to 1.15). Percentages may not total 100 because of rounding.

Table 2. Efficacy End Points.

End Point	EVT Alone (N=273)	Alteplase Followed by EVT (N=266)	Measure of Effect	Adjusted Value (95% CI)*
Primary end point: score on the modified Rankin scale at 90 days				
Median score (IQR)	3 (2 to 5)	2 (2 to 5)	Common odds ratio	0.84 (0.62 to 1.15)
Secondary end points				
Dichotomized scores on the modified Rankin scale at 90 days no. (%)				
0 or 1, not 2 to 6	44 (16.1)	41 (15.4)	Odds ratio	1.01 (0.63 to 1.63)
0 to 2, not 3 to 6	134 (49.1)	136 (51.1)	Odds ratio	0.95 (0.65 to 1.39)
0 to 3, not 4 to 6	161 (59.0)	161 (60.5)	Odds ratio	0.99 (0.66 to 1.48)
Median NIHSS score (IQR)				
After 24 hr	6 (2 to 14)	6 (1 to 14)	Beta coefficient	0.11 (–0.05 to 0.28)
After 5 to 7 days or at discharge	4 (1 to 13)	3 (1 to 9)	Beta coefficient	0.21 (0.03 to 0.38)
Median EQ-5D-5L score (IQR) at 90 days	0.8 (0.7 to 0.9)	0.8 (0.7 to 1.0)	Beta coefficient	–0.08 (–0.14 to –0.01)
Barthel Index score of 95 to 100 at 90 days no./total no. (%)	136/250 (54.4)	142/241 (58.9)	Odds ratio	0.98 (0.66 to 1.48)
Recanalization on first intracranial angiogram no./total no. (%)‖	7/250 (2.8)	9/245 (3.7)	Odds ratio	0.79 (0.42 to 1.47)
Successful reperfusion on last intracranial angiogram no./total no. (%)**	192/244 (78.7)	196/236 (83.1)	Odds ratio	0.73 (0.47 to 1.13)
Recanalization after 24 hr no./total no. (%)	172/220 (78.2)	171/202 (84.7)	Odds ratio	0.82 (0.52 to 1.28)
Median final lesion volume on follow-up imaging ml (IQR)	24 (7 to 76)	17 (5 to 72)	Beta coefficient	1.22 (0.92 to 1.63)

* Adjustments were made for age, sex, prestroke score on the modified Rankin scale, duration from onset to randomization, stroke severity (NIHSS score), and collateral status. The reported confidence intervals for secondary outcomes have not been adjusted for multiplicity, and inferences drawn from the intervals may not be reproducible. Unadjusted results are shown in Table S6 in the Supplementary Appendix.
P=0.28.
The NIHSS score was determined for survivors only. If patients were comatose, they were assigned the worst score possible. The score after 24 hours was missing for 6 patients in the EVT-alone group and 3 in the alteplase-plus-EVT group. The score after 5 to 7 days or at discharge was missing for 29 patients in the EVT-alone group and 27 in the alteplase-plus-EVT group.
The EuroQoL Group 5-Dimension 5-Level Self-Report questionnaire (EQ-5D-5L) is an ordinal scale ranging from –0.446 to 1.00 to measure quality of life. A higher score indicates a better health status. Data were missing for 23 patients in the EVT-alone group and 25 in the alteplase-plus-EVT group.
The Barthel Index quantifies performance of self-care activities of daily living, with scores ranging from 0 (severe disability) to 100 (no disability).
‖ Spontaneous recanalization was defined as the absence of treatable occlusion by the time of EVT.
** Successful reperfusion was defined as an extended Thrombolysis in Cerebral Infarction score of 2B, 2C, or 3, indicating more than 50% reperfusion of the territory downstream from the occlusion (the territory affected by the occlusion on CT angiography at baseline). All the patients who underwent groin puncture and had available reperfusion scores are included. (Additional data are provided in Table S4.)
Recanalization was defined as a modified Arterial Occlusive Lesion score of 2 or higher. The score grades recanalization on CT angiography, ranging from 0 (no recanalization) to 3 (complete recanalization).
Data were missing for 35 patients in the EVT-alone group (7 because of death or receipt of palliative care, 8 because consent was given for use of data on regular care only, 11 because of scan quality issues, and 9 for practical reasons such as patient transfer or nonadherence to the scanning protocol) and 38 patients in the alteplase-plus-EVT group (8 because of death or palliative care, 6 because consent was given for use of data on regular care only, 10 because of scan quality issues, and 14 for practical reasons such as patient transfer or nonadherence to the scanning protocol).

was slightly higher in the EVT-alone group (adjusted beta coefficient, 1.22; 95% CI, 0.92 to 1.63). Results for dichotomizations of the 90-day score on the modified Rankin scale as well as EQ-5D-5L and Barthel Index scores were similar in the two groups. Because of the lack of a pre-

Table 3. Safety End Points.*

End Point	EVT Alone (N=273)	Alteplase Followed by EVT (N=266)	Odds Ratio (95% CI)
Death within 90 days no. (%)	56 (20.5)	42 (15.8)	1.39 (0.84 2.30)
Any intracerebral hemorrhage no./total no. (%)	89/248 (35.9)	85/239 (35.6)	0.97 (0.68 1.38)
HI1	32/248 (12.9)	35/239 (14.6)	0.82 (0.50 1.34)
HI2	23/248 (9.3)	15/239 (6.3)	1.27 (0.67 2.41)
PH1	9/248 (3.6)	14/239 (5.9)	0.66 (0.32 1.39)
PH2	14/248 (5.6)	11/239 (4.6)	1.08 (0.61 1.93)
Subarachnoid hemorrhage	28/248 (11.3)	14/239 (5.9)	1.65 (0.79 3.45)
Symptomatic intracerebral hemorrhage no. (%)	16 (5.9)	14 (5.3)	1.30 (0.60 2.81)
Embolization to new territory no./total no. (%)	13/252 (5.2)	8/246 (3.3)	1.31 (0.68 2.53)
Infarction in new territory on follow-up CT or MRI no./total no. (%)	38/248 (15.3)	32/238 (13.4)	1.05 (0.69 1.60)
Small infarction	17/248 (6.9)	16/238 (6.7)	0.94 (0.54 1.63)
Substantial infarction	22/248 (8.9)	18/238 (7.6)	0.94 (0.57 1.55)
Femoral-artery false aneurysm no. (%)	3 (1.1)	3 (1.1)	1.00 (0.18 5.36)
Groin hematoma no. (%)	11 (4.0)	20 (7.5)	0.50 (0.23 1.08)

* MRI denotes magnetic resonance imaging.
Adjustments were made for age, sex, prestroke score on the modified Rankin scale, duration from onset to randomization, stroke severity (NIHSS score), and collateral status. The reported confidence intervals have not been adjusted for multiplicity, and inferences drawn from the intervals may not be reproducible. Unadjusted results are shown in Table S9.
Hemorrhage and symptomatic intracerebral hemorrhage were scored by a committee to assess serious adverse events using the Heidelberg criteria.[24] Hemorrhagic infarction type 1 (HI1) indicates scattered small petechiae without mass effect, hemorrhagic infarction type 2 (HI2) confluent petechiae without mass effect, parenchymal hematoma type 1 (PH1) a hematoma occupying less than 30% of the infarcted tissue without substantive mass effect, and parenchymal hematoma type 2 (PH2) a hematoma occupying 30% or more of the infarcted tissue with obvious mass effect.
Of the 41 cases of subarachnoid hemorrhage, 5 were major (large-volume cases caused by perforation; 3 in the EVT-alone group and 2 in the alteplase-plus-EVT group), 18 were intermediate (more extensive than Sylvian fissure but no expected clinical consequences; 12 in the EVT-alone group and 6 in the alteplase-plus-EVT group), and 18 were minor (limited to Sylvian fissure; 13 in the EVT-alone group and 5 in the alteplase-plus-EVT group).
Small infarctions were defined as lesions occupying less than 30% of one ASPECTS brain region. All small infarction lesions were seen on MRI and none were seen on CT. Of the substantial infarction lesions (≥30% of one ASPECTS brain region or multiple ASPECTS brain regions affected), 23 were scored on MRI and 17 on CT.

specified plan for adjustment of confidence intervals for multiple comparisons, no conclusions can be drawn from these secondary outcome data; however, all confidence intervals for odds ratios included 1. Results of the prespecified subgroup analyses are shown in Figure S3.

SAFETY

Mortality at 90 days was 20.5% in the EVT-alone group and 15.8% in the alteplase-plus-EVT group (adjusted odds ratio, 1.39; 95% CI, 0.84 to 2.30) (Table 3). The percentage of patients with symptomatic intracerebral hemorrhage was 5.9% and 5.3%, respectively (adjusted odds ratio, 1.30; 95% CI, 0.60 to 2.81). The incidence of any intracranial bleeding was approximately 35% in both groups. The results regarding other safety end points and procedural complications were similar in the two groups (Table S8).

DISCUSSION

In contrast to some previous trials involving Asian patients with anterior-circulation stroke, we did not find that EVT alone was noninferior or superior to intravenous alteplase combined with EVT with regard to functional outcome at 90 days. Our trial population was European and was limited to patients presenting directly to centers providing EVT, similar to the populations in

some previous trials (DIRECT-MT [Direct Intra-arterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: a Multicenter Randomized Clinical Trial], DEVT [Direct Endovascular Thrombectomy versus Combined IVT and Endovascular Thrombectomy for Patients with Acute Large Vessel Occlusion in the Anterior Circulation], and SKIP [Direct Mechanical Thrombectomy in Acute LVO Stroke]),[9-11] and our trial did not include patients who were given alteplase at one hospital and transferred to another hospital for EVT. The mortality was slightly higher in the EVT-alone group but did not differ substantially between the two groups, and the incidence of symptomatic intracerebral hemorrhage was similar in the two groups.

The incidence of functional independence and endovascular reperfusion grades in both groups in our trial were similar to those in the DIRECT-MT, DEVT, and SKIP trials. Yet in our trial, patients had shorter times from stroke onset to administration of alteplase and shorter times from stroke onset to groin puncture for EVT.[9-11] These findings may be attributable to our use of deferred consent and to shorter travel distances to hospitals (than, for instance, in China), prehospital triage systems, and in-hospital logistics. Furthermore, our trial population differed from those in the other trials in that there were fewer patients with atrial fibrillation or intracranial atherosclerosis, and we included patients with proximal M2 occlusions who were infrequently included in the previous trials. In addition, we allowed for rescue intravenous alteplase in the EVT-alone group if reperfusion did not occur; this was administered to 19 patients in our trial.

The current trial was partly based on the hypothesis that omitting intravenous alteplase before EVT would reduce the risk of intracerebral hemorrhage and thereby improve outcomes. The difference in mortality between the groups in our trial cannot be explained by differences in the incidences of intracerebral hemorrhage.

Our trial had limitations. First, our results apply only to patients presenting directly to a center capable of EVT. In addition, times from stroke onset to hospital arrival were relatively short, which limits the generalizability of our results to care settings with longer times to hospital arrival. Second, our enrolled population had small between-group differences with respect to atrial fibrillation, age, and occlusion location, with more prognostically unfavorable values in the EVT-alone group. These differences may have affected the trial results in favor of the alteplase-plus-EVT group. Third, our trial protocol initially defined stent-retrievers as first-line techniques for EVT because they were considered to be the approach supported by evidence at the time.[2,3] During the trial, aspiration devices were increasingly used in clinical practice and were adopted. Fourth, our trial had an open-label design, which may have influenced postprocedural patient care. Fifth, we used deferred consent in order to not delay alteplase infusion or EVT treatments for stroke, which made an intention-to-treat analysis difficult (this applied to only eight patients).

In this European trial of anterior-circulation stroke, EVT alone was neither superior nor noninferior to intravenous alteplase followed by EVT with respect to functional outcomes at 90 days in patients presenting directly to centers capable of providing both treatments.

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APPENDIX

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