ORIGINAL ARTICLE

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke

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ABSTRACT

BACKGROUND

Among patients with a proximal vessel occlusion in the anterior circulation, 60 to 80% of patients die within 90 days after stroke onset or do not regain functional independence despite alteplase treatment. We evaluated rapid endovascular treatment in addition to standard care in patients with acute ischemic stroke with a small infarct core, a proximal intracranial arterial occlusion, and moderate-to-good collateral circulation.

METHODS

We randomly assigned participants to receive standard care (control group) or standard care plus endovascular treatment with the use of available thrombectomy devices (intervention group). Patients with a proximal intracranial occlusion in the anterior circulation were included up to 12 hours after symptom onset. Patients with a large infarct core or poor collateral circulation on computed tomography (CT) and CT angiography were excluded. Workflow times were measured against predetermined targets. The primary outcome was the score on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]) at 90 days. A proportional odds model was used to calculate the common odds ratio as a measure of the likelihood that the intervention would lead to lower scores on the modified Rankin scale than would control care (shift analysis).

RESULTS

The trial was stopped early because of efficacy. At 22 centers worldwide, 316 participants were enrolled, of whom 238 received intravenous alteplase (120 in the intervention group and 118 in the control group). In the intervention group, the median time from study CT of the head to first reperfusion was 84 minutes. The rate of functional independence (90-day modified Rankin score of 0 to 2) was increased with the intervention (53.0%, vs. 29.3% in the control group; P<0.001). The primary outcome favored the intervention (common odds ratio, 2.6; 95% confidence interval, 1.7 to 3.8; P<0.001), and the intervention was associated with reduced mortality (10.4%, vs. 19.0% in the control group; P=0.04). Symptomatic intracerebral hemorrhage occurred in 3.6% of participants in intervention group and 2.7% of participants in control group (P=0.75).

CONCLUSIONS

Among patients with acute ischemic stroke with a proximal vessel occlusion, a small infarct core, and moderate-to-good collateral circulation, rapid endovascular treatment improved functional outcomes and reduced mortality. (Funded by Covidien and others; ESCAPE ClinicalTrials.gov number, NCT01778335.)

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*A complete list of sites and investigators in the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial is provided in the Supplementary Appendix, available at NEJM.org.

ISCHEMIC STROKE IS A DEVASTATING CONDItion with a high burden of neurologic disability and death. As a systemic treatment, intravenous alteplase has been shown to be better than conservative care.[1,2] Among patients with a proximal vessel occlusion in the anterior circulation, 60 to 80% of patients die within 90 days after stroke onset or do not regain functional independence despite alteplase treatment.[3,4] The major reason for the limited efficacy of alteplase is the modest rate of early reperfusion among patients with a large-vessel occlusion.[5,6]

Local treatment of large-vessel occlusion began with intraarterial delivery of thrombolytic drugs.[7] The Prolyse in Acute Cerebral Thromboembolism (PROACT) II study was the first positive trial of endovascular treatment involving patients with angiographically visualized occlusion of the middle cerebral artery.[8] Unfortunately, subsequent trials did not confirm the clinical benefit even with the addition of firstgeneration thrombectomy devices.[3,9,10] Key lessons learned from these previous trials are the need for proof of proximal vessel occlusion,[11] rapid and effective imaging methods to exclude patients with a large infarct core,[12-14] an efficient workflow to achieve fast recanalization,[15,16] and high reperfusion rates.[17-19]

Recent studies have shown the superiority of retrievable stents over the previous generation of thrombectomy devices.[17,18] The recently reported Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) used this technology, and the results of that trial showed clinical benefit with endovascular treatment.[4] The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial was designed to test whether patients with acute ischemic stroke, who were selected on the basis of results of computed tomography (CT) and CT angiography (CTA), would benefit from rapid endovascular treatment involving contemporary endovascular techniques.[20]

METHODS

TRIAL DESIGN

The ESCAPE trial was a multicenter, prospective, randomized, open-label, controlled trial with blinded outcome evaluation (PROBE design).[20] Participants were assigned, in a 1:1 ratio, to receive endovascular treatment plus guideline-based care (intervention group) or guideline-based care alone (control group) (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). This academicinvestigator–initiated trial was designed to answer a practical question regarding a patient with acute ischemic stroke who has just undergone neurovascular imaging with noncontrast CT and CTA: "Should this patient undergo endovascular thrombectomy?" (Fig. S3 in the Supplementary Appendix).

The trial was monitored by an independent data and safety monitoring board. The study funders, including Covidien, were not involved in the design or conduct of the study, the preparation or review of the protocol, the collection or analysis of the data, or the preparation or review of the manuscript. All the authors collected data, provided comments on the analysis, contributed to the writing of the manuscript, and were independent of the sponsors. All the authors vouch for the accuracy and completeness of the data and data analyses and for the fidelity of this report to the study protocol, available at NEJM.org.

Sites were selected for participation after visits by the principal investigators and documentation of fast treatment times and efficient workflow. The principal investigator at each site signed a formal letter stating a commitment to attempt to enroll consecutive patients who were eligible for the ESCAPE trial.[21] The ethics board at each site approved the trial. In jurisdictions where it was permitted, the consent process was deferred when the participant lacked the capacity to provide consent and a legally authorized representative was unavailable.

Randomization was performed with the use of a real-time, dynamic, Internet-based, randomized minimization procedure (minimal sufficient balance method)[22] to achieve distribution balance with regard to age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating greater stroke severity), site of arterial occlusion, baseline Alberta Stroke Program Early Computed Tomography Score (ASPECTS), and status with respect to intravenous alteplase treatment. The ASPECTS scale is a 10-point scoring system to quantify early ischemic changes in the middle-cerebral-artery territory, with a score of 10 indicating normal and 1 point subtracted for each abnormal region (details are available at www.aspectsinstroke.com).[23,24]

PARTICIPANTS

Eligible participants were adults (no upper-age limit) with a disabling ischemic stroke who had been functioning independently in the community (score on the Barthel Index [range, 0 to 100, with higher scores indicating a greater ability to complete activities of daily living] ≥90) before the stroke. Enrollment could occur up to 12 hours after the onset of stroke symptoms. Noncontrast CT and CTA (preferably multiphase) were performed to identify participants with a small infarct core, an occluded proximal artery in the anterior circulation, and moderate-to-good collateral circulation.[14,25-28] Multiphase CTA is less vulnerable to patient motion than CT perfusion, requires no additional contrast, and allows for quick determination of collateral status[12] (Fig. S2 in the Supplementary Appendix). The use of magnetic resonance imaging for patient selection was discouraged. A small infarct core was defined as an ASPECTS of 6 to 10. Proximal artery occlusion in the anterior circulation was defined as occlusion of the middle-cerebral-artery trunk and its immediate branches, with or without intracranial occlusion of the internal carotid artery (Fig. S4 in the Supplementary Appendix). Moderate-to-good collateral circulation was defined as the filling of 50% or more of the middle-cerebral-artery pial arterial circulation on CTA (preferably on multiphase CTA).

Imaging was performed at the endovascular center; for patients transferred from other hospitals, imaging was repeated. Before and during screening, participants were treated with intravenous alteplase when clinically appropriate as part of standard care (Fig. S3 in the Supplementary Appendix). We did not keep a log of patients who were screened for the trial.[29]

TREATMENTS

Participants in the intervention group underwent rapid endovascular treatment. A cerebral angiogram was obtained. The neurointerventionist used available thrombectomy devices to achieve reperfusion. The use of retrievable stents was recommended. During thrombus retrieval, suction through a balloon guide catheter in the relevant internal carotid artery was also recommended. The control group received the current standard of care as described in the Canadian or local guidelines for the management of acute stroke[30,31] (see the Methods section in the Supplementary Appendix). Participants in both groups received intravenous alteplase within 4.5 hours after the onset of stroke symptoms if they met accepted local guidelines for intravenous alteplase treatment.

Weekly monitoring of imaging and treatment speed, with regular feedback to sites by teleconference, ensured adherence to participant eligibility criteria and workflow metrics. Guidance on rapid, effective endovascular treatment and high-quality imaging methods was provided. The target time from study noncontrast CT to groin puncture was 60 minutes or less and from study noncontrast CT to first reperfusion (defined as first reflow in the middle cerebral artery) was 90 minutes or less. These aggressive targets were chosen to emphasize speed and ensure rapid imaging acquisition and interpretation, quick transfer of patients to the angiography suite, and fast reperfusion. If there were clear patient-related factors (e.g., vessel tortuosity) or workflow factors (e.g., unavailability of the intervention team) that would prevent meeting the time targets, it was recommended that patients not be enrolled.

CLINICAL ASSESSMENTS AND OUTCOMES

All participants had standard assessments of demographic characteristics, medical history, laboratory values, and stroke severity (NIHSS score). Details of the assessments have been published previously[20] and are also available in the study protocol. The primary outcome — the score on the modified Rankin scale at 90 days after randomization — was assessed by trained personnel who were unaware of the treatment-group assignments. The modified Rankin scale is a graded interval scale (range, 0 [no symptoms] to 6 [death]) for the assessment of neurologic functional disability.[32] Secondary and safety outcomes included early recanalization and reperfusion, intracranial hemorrhage, angiographic complications, neurologic disability at 90 days, and death. Interpretation of the imaging was performed at an external core laboratory by personnel who were unaware of the treatment-group assignments (when they interpreted the CT images), clinical data, and outcomes. External, independent clinical monitors validated the clinical data.

STATISTICAL ANALYSIS

The trial was powered to detect a shift in the distribution of scores on the modified Rankin scale at 90 days between the intervention and control groups, with scores of 5 (bedbound with severe disability) and 6 (death) combined, with

the assumption that the differential effect would lead to a common odds ratio (indicating the odds of improvement of 1 point on the modified Rankin scale) of 1.8. A total required sample of 500 participants was anticipated. One formal interim analysis after the enrollment of 300 participants was planned. The stopping rule for efficacy was defined with the use of O'Brien–Fleming boundaries on the binary outcome of a modified Rankin score at 90 days of 0 to 2 versus 3 to 6.[20] The primary analysis was unadjusted and was performed in the intention-to-treat population. P values of less than 0.05 were considered to indicate statistical significance, and all tests of hypotheses were two-sided. No adjustments were made for multiple comparisons. Adjusted estimates of effect were calculated, with adjustment for age, sex, baseline NIHSS score, baseline ASPECTS, location of occlusion (internal carotid artery plus middle cerebral artery vs. middle cerebral artery only), and status with respect to intravenous alteplase treatment (yes vs. no). The assessment of effect modification (heterogeneity of treatment effect) was performed with the inclusion of multiplicative interaction terms. All analyses were performed with the use of Stata software, version 12.1 (StataCorp). Figures were drawn with the use of both Stata software, version 12.1, and R software (R Development Core Team 2014, www.r-project.org). Further details are provided in the statistical analysis plan (available at NEJM.org).

Table 1. Baseline Characteristics and Process Measures.*

Variable	Intervention (N = 165)	Control (N = 150)
Demographic characteristics		
Age — yr		
Median	71	70
Interquartile range	60–81	60–81
Female sex — no. (%)	86 (52.1)	79 (52.7)
White race — no. (%)†	144 (87.3)	131 (87.3)
Medical history — no. (%)		
Hypertension	105 (63.6)	108 (72.0)
Diabetes mellitus	33 (20.0)	39 (26.0)
Atrial fibrillation	61 (37.0)	60 (40.0)
Clinical characteristics		
NIHSS score‡		
Median	16	17
Interquartile range	13–20	12–20
Systolic blood pressure at hospital arrival — mm Hg		
Median	147	146
Interquartile range	131–159	125–169
Glucose level at hospital arrival — mmol/liter§		
Median	6.6	6.7
Interquartile range	5.8–7.7	5.7–7.8
Imaging characteristics		
ASPECTS on CT — median (interquartile range)¶	9 (8–10)	9 (8–10)
Location of occlusion on CTA — no./total no. (%)‖		
ICA with involvement of the M1 middle-cerebral-artery segment	45/163 (27.6)	39/147 (26.5)
M1 or all M2 middle-cerebral-artery segments	111/163 (68.1)	105/147 (71.4)
Single M2 middle-cerebral-artery segment	6/163 (3.7)	3/147 (2.0)
Ipsilateral cervical carotid occlusion — no. (%)	21 (12.7)	19 (12.7)

Variable	Intervention (N = 165)	Control (N = 150)
Process times — min**		
Stroke onset to randomization		
Median	169	172
Interquartile range	117–285	119–284
Stroke onset to study CT		
Median	134	136
Interquartile range	77–247	76–238
Stroke onset to start of IV alteplase		
Median	110	125
Interquartile range	80–142	89–183
Study CT to groin puncture		
Median	51	
Interquartile range	39–68	
Study CT to first reperfusion††		
Median	84	
Interquartile range	65–115	
Stroke onset to first reperfusion††		
Median	241	
Interquartile range	176–359	
Treatment with IV alteplase — no. (%)	120 (72.7)	118 (78.7)

Table 1. (Continued.)

* The intervention group was assigned to endovascular treatment plus standard care, and the control group was assigned to standard care alone. CT denotes computed tomography, CTA CT angiography, ICA internal carotid artery, and IV intravenous.

† Race was self-reported.

‡ Scores on National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits.

§ To convert the values to milligrams per deciliter, divide by 0.05551.

¶ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is an imaging measure of the extent of ischemic stroke. Scores ranges from 0 to 10, with higher scores indicating a smaller infarct core (details are available at www.aspectsinstroke.com).

‖ In one participant in the intervention group, the location of the occlusion on CTA was not determined by the core laboratory. Occlusion of the ICA with involvement of the M1 middle-cerebral-artery segment could occur with or without involvement of the A1 anterior-cerebral-artery segment (see Fig. S4 in the Supplementary Appendix). The M1 middle-cerebral-artery segment extends from the origin to the site of bifurcation or trifurcation (the anterior temporal artery is considered a branch of the M1 segment). The M2 middle-cerebral-artery segments extend from the site of bifurcation or trifurcation to the origin of the cortical branches.

** For the time from stroke onset to the start of IV alteplase, data were missing for 1 patient in the intervention group. For the time from study CT to groin puncture, 161 patients were included in the analysis. For the time from study CT to first reperfusion and the time from stroke onset to first reperfusion, 145 patients were included in the analysis.

†† First reperfusion was defined as the first visualization of reflow in the middle cerebral artery, usually on deployment of a retrievable stent.
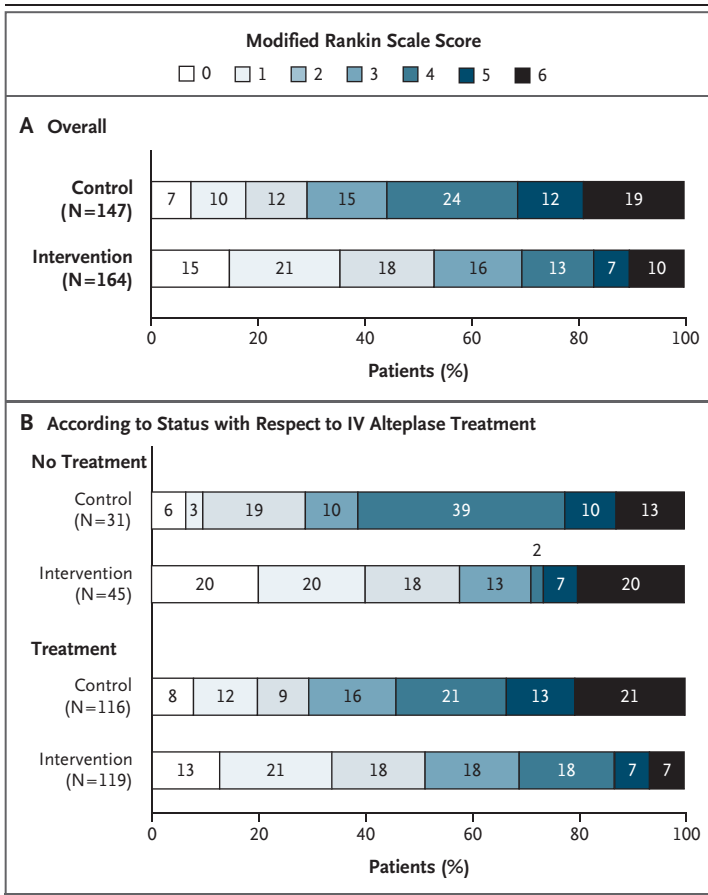
RESULTS

EARLY TERMINATION OF THE STUDY

An unplanned interim analysis was conducted after the release of the MR CLEAN results, which showed efficacy of endovascular therapy (see the Methods section in the Supplementary Appendix). The ESCAPE trial was stopped early on the advice of the data and safety monitoring board because the prespecified boundary for efficacy had been crossed.

PATIENTS

At 22 centers in Canada (11 centers), the United States (6), South Korea (3), Ireland (1), and the

Modified Rankin Scale Score

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ■ 6

A Overall

B According to Status with Respect to IV Alteplase Treatment

Figure 1. Scores on the Modified Rankin Scale at 90 Days in the 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. Panel A shows the distribution of scores at 90 days in the intervention and control groups in the overall trial population. A significant difference between the intervention and control groups was noted in the overall distribution of scores (unadjusted common odds ratio, indicating the odds of improvement of 1 point on the modified Rankin scale, 2.6; 95% confidence interval, 1.7 to 3.8), favoring the intervention. Panel B shows the distribution of scores at 90 days in the intervention and control groups according to status with respect to intravenous (IV) alteplase treatment. In this analysis, there was no evidence of heterogeneity of effect (P=0.89 for interaction by the Wald test).

United Kingdom (1), a total of 316 participants underwent randomization before the trial was stopped: 165 participants were assigned to the intervention group, 150 participants were assigned to the control group, and 1 participant was excluded owing to improper consent procedures. The trial enrolled 1.44 participants per center per month from February 2013 through October 2014. One participant in the control group crossed over to receive endovascular treatment. In the intervention group, 14 participants did not receive any interventional therapy. Four participants (1.3%) were lost to follow-up; missing data on outcomes in these participants were not imputed (Fig. S1 in the Supplementary Appendix).

Baseline characteristics were similar in the two treatment groups (Table 1, and Table S1 in the Supplementary Appendix). Imaging protocol violations, identified by personnel who interpreted the images at the core laboratory, occurred in 26 participants (8.3%): 11 of 308 participants in whom the ASPECTS could be evaluated (3.6%) had a score of less than 6 on the ASPECTS scale, 20 of 315 participants (6.3%) had poor collateral circulation, and 14 of 315 participants (4.4%) had inappropriate target-vessel occlusion (some participants had >1 protocol violation). Collateral circulation was assessed with the use of multiphase CTA in a majority of participants. A total of 56 participants (17.8%) were enrolled with deferral of consent procedures. Monitoring of appropriate source documentation materials (with regard to informed consent, inclusion and exclusion criteria, randomization information, demographic characteristics, and assessments at baseline [NIHSS score and Barthel Index score] and at day 90 [modified Rankin score, NIHSS score, and Barthel Index score]) was completed for all randomly assigned participants.

PRIMARY OUTCOME

Analysis of the primary end point showed a common odds ratio (indicating the odds of improvement of 1 point on the modified Rankin scale) of 2.6 (95% confidence interval [CI], 1.7 to 3.8) favoring the intervention (P<0.001) (Fig. 1A and Table 2). The median 90-day modified Rankin score was 2 in the intervention group and 4 in the control group (P<0.001). The proportion of patients with a modified Rankin score of 0 to 2 at 90 days was 53.0% in the intervention group and 29.3% in the control group (rate ratio, 1.8; 95% CI, 1.4 to 2.4; P<0.001). Mortality at 90 days was 10.4% in the intervention group and 19.0% in the control group (rate ratio, 0.5; 95% CI, 0.3 to 1.0; P=0.04) (Fig. S5 in the Supplementary Appendix). The rate of symptomatic intracerebral hemorrhage was 3.6% in the intervention group and 2.7% in the control group (rate ratio, 1.4; 95% CI, 0.4 to 4.7; P=0.75). Device-related or procedural complications were observed in 18 patients: 4 had a

Table 2. Primary and Secondary Efficacy Outcomes.

Outcome	Intervention (N = 165)	Control (N = 150)	Difference (95% CI)*	Effect Variable	Unadjusted Value (95% CI)	Adjusted Value (95% CI)†
Primary outcome: modified Rankin score at 90 days‡				Common odds ratio	2.6 (1.7–3.8)	3.1 (2.0–4.7)
Modified Rankin score of 0–2 at 90 days — no./total no. (%)§	87/164 (53.0)	43/147 (29.3)	23.8 (13.2–34.4)	Rate ratio	1.8 (1.4–2.4)	1.7 (1.3–2.2)
NIHSS score of 0–2 at 90 days — no./total no. (%)	79/153 (51.6)	31/134 (23.1)	28.4 (17.8–39.2)	Rate ratio	2.2 (1.6–3.2)	2.1 (1.5–3.0)
Barthel Index score of 95–100 at 90 days — no./total no. (%)¶	94/163 (57.7)	49/146 (33.6)	24.1 (13.3–34.9)	Rate ratio	1.7 (1.3–2.2)	1.7 (1.3–2.2)
TICI score of 2b or 3 at final angiogram — no./total no. (%)‖	113/156 (72.4)					
Modified AOL score of 2 or 3 — no./total no. (%)**		43/138 (31.2)				
NIHSS score at 24 hours — median (interquartile range)††	6 (3–14)	13 (6–18)		Beta coefficient	4.0 (2.2–5.8)	4.1 (2.6–5.6)
NIHSS score at 90 days — median (interquartile range)††	2 (1–8)	8 (3–19)		Beta coefficient	6.5 (3.2–9.8)	6.5 (3.5–9.6)
EQ-5D visual-analogue scale score at 90 days — median (interquartile range)††‡‡	80 (60–90)	65 (50–80)		Beta coefficient	9.4 (3.5–15.2)	9.9 (3.8–16.0)

* Differences (intervention group – control group) are shown as percentage points.
† Adjusted estimates were calculated with the use of multiple regression analyses. Estimates were adjusted for age, sex, baseline NIHSS score, baseline ASPECTS, occlusion location, and status with respect to intravenous alteplase treatment, as prespecified in the protocol and statistical analysis plan.
‡ The primary analysis involved 164 participants in the intervention group and 147 participants in the control group. Scores on the modified Rankin scale of functional disability range from 0 (no symptoms) to 6 (death). The common odds ratio was estimated from an ordinal logistic-regression model and indicates the odds of improvement of 1 point on the modified Rankin scale, with a common odds ratio greater than 1 favoring the intervention. The proportional odds assumption was tested and found to be valid.
§ A modified Rankin score of 0 to 2 indicates functional independence.
¶ The Barthel Index is an ordinal scale for measuring performance of activities of daily living. Scores range from 0 to 100, with 0 indicating severe disability and 95 or 100 no disability that interferes with daily activities.
‖ A Thrombolysis in Cerebral Infarction (TICI) score of 2b or 3 indicates successful reperfusion (see Table S3 in the Supplementary Appendix).
** A modified Arterial Occlusive Lesion (AOL) score of 2 or 3 indicates partial or complete recanalization (see Table S3 in the Supplementary Appendix).
†† Treatment effect was estimated with the use of simple linear regression.
‡‡ The EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) visual-analogue scale is a continuous scale measure of self-reported quality of life. Scores range from 0 to 100, with 0 indicating the worst possible quality of life and 100 the best possible quality of life.

serious adverse event and 14 had a nonserious adverse event (Table 3, and Table S2 in the Supplementary Appendix).

SECONDARY OUTCOMES AND SUBGROUP ANALYSES

Secondary clinical and imaging end points favored the intervention group. The rate of patients with a score on the Barthel Index of 95 to 100 at 90 days was 57.7% in the intervention group versus 33.6% in the control group, the rate of patients with a 90-day NIHSS score of 0 to 2 was 51.6% versus 23.1%, and the median 90-day score on the EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) visual-analogue scale (range,

0 to 100, with higher scores indicating better quality of life) was 80 versus 65 (Table 2).

There was no evidence of heterogeneity of effect across any of the prespecified subgroups (defined according to age, sex, baseline NIHSS score, baseline ASPECTS, occlusion location, and status with respect to alteplase treatment) or according to the presence or absence of cervical carotid occlusion. All variables showed a direction of effect in favor of the intervention (Fig. 2, and Fig. S6 in the Supplementary Appendix). However, the absolute proportion of good outcomes varied substantially according to subgroup (Fig. 1B, and Fig. S7 in the Supplementary Appendix).

Table 3. Reported Serious Adverse Events.

Event	Intervention (N = 165)	Control (N = 150)	Difference (95% CI)*	Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)†
Death — no./total no. (%)	17/164 (10.4)	28/147 (19.0)	8.6 (0.8 to 16.6)	0.5 (0.3 to 1.0)	0.5 (0.3 to 0.8)
Large or malignant middle-cerebral-artery stroke — no. (%)‡	8 (4.8)	16 (10.7)	5.8 (0.1 to 11.7)	0.5 (0.2 to 1.0)	0.3 (0.1 to 0.7)
Symptomatic intracerebral hemorrhage — no. (%)‡§	6 (3.6)	4 (2.7)	1.0 (−2.9 to 4.8)	1.4 (0.4 to 4.7)	1.2 (0.3 to 4.6)
Hematoma at access site — no. (%)¶	3 (1.8)	0			
Perforation of the middle cerebral artery — no. (%)	1 (0.6)	0			

* Differences (intervention group – control group) are shown as percentage points.
† Adjusted estimates were calculated with the use of multiple regression analyses. Estimates were adjusted for age, sex, baseline NIHSS score, baseline ASPECTS, occlusion location, and status with respect to intravenous alteplase treatment, as prespecified in the protocol and statistical analysis plan.
‡ Two hemicraniectomy procedures were performed. The indications for hemicraniectomy were malignant middle-cerebral-artery ischemic stroke (one patient in the control group) and symptomatic intracerebral hemorrhage (one patient in the intervention group).
§ Symptomatic intracerebral hemorrhage was clinically determined at the study site.
¶ Hematoma occurred in two participants at the site of groin puncture. Neck hematoma occurred in the single participant in whom direct carotid access was used, after femoral access was unsuccessful.

A total of 49 patients underwent randomization 6 or more hours after stroke onset; in the analysis of a modified Rankin score of 0 to 2 at 90 days, the direction of effect favored the intervention in these patients (rate ratio, 1.7; 95% CI, 0.7 to 4.0), but the between-group difference was not significant.

Of 165 participants assigned to the intervention group, 151 (91.5%) underwent endovascular treatment, and 120 (72.7%) received intravenous alteplase. General anesthesia was used in 15 participants (9.1%). Retrievable stents were used in 130 of the 151 participants (86.1%) who underwent an endovascular procedure; 100 of these 130 participants (77.0%) received a Solitaire stent (Covidien). In the intervention group, the median time from symptom onset to first reperfusion was 241 minutes (interquartile range, 176 to 359), the median time from study CT to first reperfusion was 84 minutes (interquartile range, 65 to 115), and the median time from groin puncture to first reperfusion was 30 minutes (interquartile range, 18 to 46). Successful reperfusion (as defined by a core-laboratory–adjudicated Thrombolysis in Cerebral Infarction [TICI] score of 2b or 3, indicating complete filling of the expected vascular territory) was observed in 113 of 156 participants (72.4%) in the intervention group: 79 of 112 participants (70.5%) who received intravenous alteplase and 34 of 44 participants (77%) who did not. (For details on the TICI scale, see Table 3 in the Supplementary Appendix.)

In the control group, follow-up CTA was performed in 138 participants (median time from symptom onset to follow-up CTA, 425 minutes [interquartile range, 355 to 564]). Successful recanalization (as defined by a core-laboratory–adjudicated modified Arterial Occlusive Lesion score of 2 or 3 on CTA, indicating partial or complete recanalization of the occluded artery) was observed in 43 of 138 participants (31.2%): 41 of 110 (37.3%) who received intravenous alteplase and 2 of 28 (7%) who did not. (For details on the modified Arterial Occlusive Lesion scale, see Table S3 in the Supplementary Appendix.)

DISCUSSION

We found that among participants with acute ischemic stroke with a small infarct core, a proximal intracranial occlusion in the anterior circulation, and moderate-to-good intracranial collateral circulation, rapid endovascular treatment improved the clinical outcome and reduced mortality. The trial confirms the benefit of endovascular treatment reported recently in the MR CLEAN trial.[4]

The ESCAPE trial attempted to deliver rapid endovascular therapy to patients who were selected for inclusion on the basis of imaging. Post hoc analysis of the Interventional Management of Stroke (IMS) III trial and the Solitaire FR Thrombectomy for Acute Revascularization (STAR) trial showed that achieving faster reperfusion, as
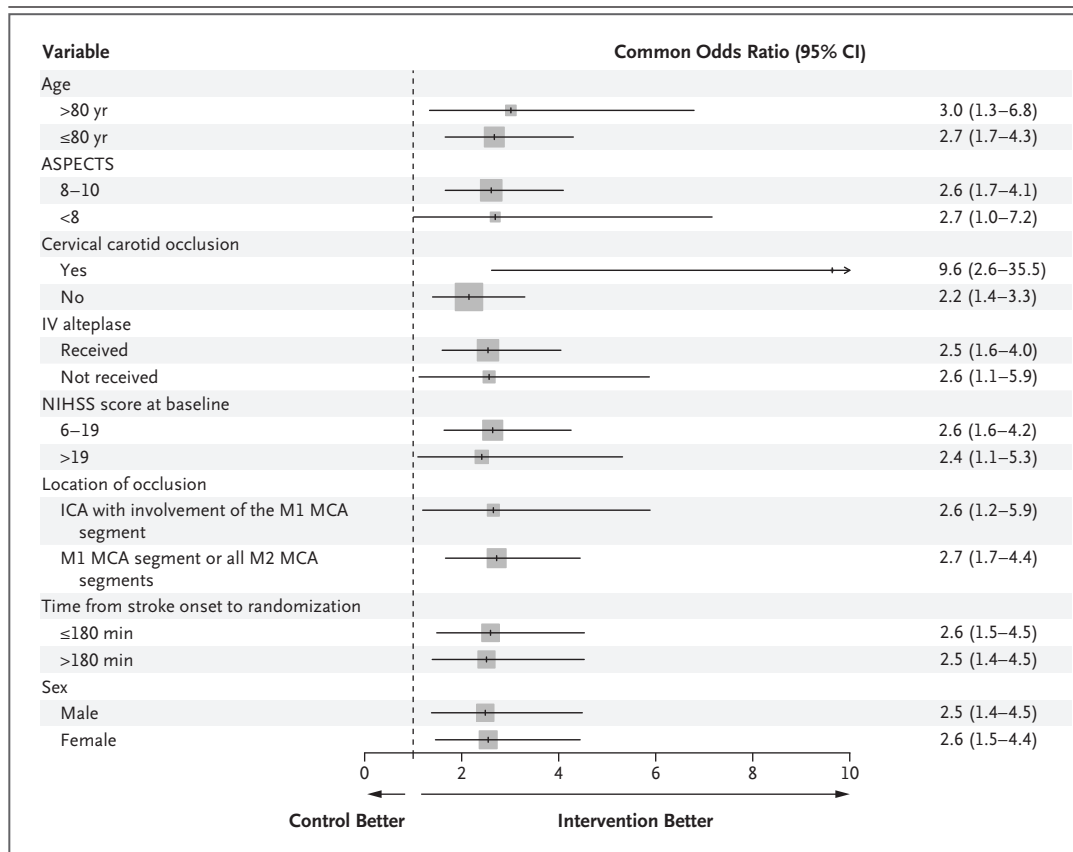
Figure 2. Subgroup Analyses.

A forest plot shows that the difference in the primary clinical outcome (common odds ratio indicating the odds of improvement of one point on the modified Rankin scale at 90 days, analyzed with the use of ordinal logistic regression) favored the intervention group across all prespecified subgroups. The thresholds for age and National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating more severe neurologic deficits) were chosen at the 75th percentile, and the threshold for time from stroke onset to randomization was chosen just above the median. The threshold for the Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range, 0 to 10, with higher scores indicating a smaller infarct core) was prespecified. For cervical carotid occlusion, P=0.049 for interaction by the Wald test. Other P values were greater than 0.10 for interaction. ICA denotes internal carotid artery, and MCA middle cerebral artery.

compared with slower reperfusion, was associated with a better clinical outcome.[16,33] The ESCAPE trial achieved shorter interval times than those seen in past trials, with a median time from study noncontrast CT to first reperfusion of 84 minutes. A prespecified efficiency target for the time from noncontrast CT to reperfusion encouraged fast image acquisition and interpretation and fast decision making.[16,34-37] Critical to the achievement of rapid treatment was parallel decision making and action. For example, participants in the intervention group underwent groin puncture while alteplase was being infused, and complete reperfusion was achieved in some participants before the alteplase infusion was fin-

ished. The primary emphasis was on achieving early reperfusion.[15,16,34,35]

Imaging-related selection criteria focused on the population with a small infarct core at baseline, which was defined by both modest early ischemic change on noncontrast CT and moderate-to-good collateral circulation distal to the occlusion.[26] A new technique of collateral assessment, multiphase CTA, was used in a majority of patients (Fig. S2 in the Supplementary Appendix).[12] This imaging approach resulted in a low number of imaging protocol violations and enabled the meeting of workflow time targets.

There was no evidence of heterogeneity of treatment effect across prespecified subgroups.

Endovascular treatment appeared to benefit all ages (the oldest person enrolled in the trial was 93 years of age), both sexes, patients with moderate strokes and those with severe strokes, patients who received intravenous alteplase and those who did not, and patients with and those without occlusion in the internal carotid artery (Fig. 2, and Fig. S6 in the Supplementary Appendix). Although eligibility criteria allowed enrollment up to 12 hours after symptom onset, the median time from symptom onset to first reperfusion was 241 minutes. A total of 49 participants (15.5%) underwent randomization 6 or more hours after symptom onset, and the study was not powered to assess endovascular therapy among patients presenting 6 to 12 hours after symptom onset.

The incidence of asymptomatic hemorrhagic infarction was greater in the intervention group than in the control group (Table S2 in the Supplementary Appendix), possibly owing to early reperfusion.[38] The rate of more serious parenchymal hematomas or symptomatic hemorrhage was not higher in the intervention group than in the control group. Device-related or procedural complications were uncommon.

MR CLEAN and the ESCAPE trial showed benefit and low complication rates with endovascular treatment that was performed predominantly with retrievable stents. Factors that distinguish the ESCAPE trial from MR CLEAN and prior trials of endovascular treatment for stroke include the use of imaging to exclude participants with a large infarct core and poor collateral circulation, a shorter interval from symptom onset to treatment initiation, a low rate of general anesthesia (9% in the ESCAPE trial vs. 38% in MR CLEAN), and a higher rate of successful reperfusion (TICI score of 2b or 3). The longer time from alteplase administration to randomization (approximately 114 minutes) in MR CLEAN indicated that most patients underwent randomization after the alteplase infusion was completed.[4] These differences may account for the higher proportions of good outcomes and the larger effect size observed in the ESCAPE trial.

There are limitations of our study. First, we purposefully did not require screening logs (which tend to yield poor-quality data) and cannot provide an estimate of how many patients were ineligible on the basis of imaging criteria. Second, a majority of participants were enrolled at selected endovascular centers that are capable of implementing efficient workflow and imaging processes. This level of efficiency and expertise is not currently widespread, which limits the immediate generalizability of our results. Although the time targets used in our trial may appear daunting, the history of intervention for acute coronary syndromes suggests that such efficiency in workflow is widely attainable.[35,39,40]

In conclusion, the ESCAPE trial, in which fast and efficient workflow, innovative imaging, and effective thrombectomy devices were used, provides evidence of the benefit of endovascular treatment in patients with moderate-to-severe ischemic stroke.

APPENDIX

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