ORIGINAL ARTICLE

Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection

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ABSTRACT

BACKGROUND

Trials of endovascular therapy for ischemic stroke have produced variable results. We conducted this study to test whether more advanced imaging selection, recently developed devices, and earlier intervention improve outcomes.

METHODS

We randomly assigned patients with ischemic stroke who were receiving 0.9 mg of alteplase per kilogram of body weight less than 4.5 hours after the onset of ischemic stroke either to undergo endovascular thrombectomy with the Solitaire FR (Flow Restoration) stent retriever or to continue receiving alteplase alone. All the patients had occlusion of the internal carotid or middle cerebral artery and evidence of salvageable brain tissue and ischemic core of less than 70 ml on computed tomographic (CT) perfusion imaging. The coprimary outcomes were reperfusion at 24 hours and early neurologic improvement (≥8-point reduction on the National Institutes of Health Stroke Scale or a score of 0 or 1 at day 3). Secondary outcomes included the functional score on the modified Rankin scale at 90 days.

RESULTS

The trial was stopped early because of efficacy after 70 patients had undergone randomization (35 patients in each group). The percentage of ischemic territory that had undergone reperfusion at 24 hours was greater in the endovascular-therapy group than in the alteplase-only group (median, 100% vs. 37%; P<0.001). Endovascular therapy, initiated at a median of 210 minutes after the onset of stroke, increased early neurologic improvement at 3 days (80% vs. 37%, P=0.002) and improved the functional outcome at 90 days, with more patients achieving functional independence (score of 0 to 2 on the modified Rankin scale, 71% vs. 40%; P=0.01). There were no significant differences in rates of death or symptomatic intracerebral hemorrhage.

CONCLUSIONS

In patients with ischemic stroke with a proximal cerebral arterial occlusion and salvageable tissue on CT perfusion imaging, early thrombectomy with the Solitaire FR stent retriever, as compared with alteplase alone, improved reperfusion, early neurologic recovery, and functional outcome. (Funded by the Australian National Health and Medical Research Council and others; EXTEND-IA ClinicalTrials.gov number, NCT01492725, and Australian New Zealand Clinical Trials Registry number, ACTRN12611000969965.)

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*A complete list of investigators in the Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND-IA) trial is provided in the Supplementary Appendix, available at NEJM.org.

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The results of the multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial,[1] which showed reduced disability among patients with ischemic stroke who were treated with endovascular thrombectomy in addition to standard care, represent an advance in stroke care. The MR CLEAN study followed several trials that had neutral findings with respect to the use of endovascular thrombectomy.[2-4] In the largest of these trials, the Interventional Management of Stroke 3 (IMS-3) study, investigators compared the administration of 0.9 mg of alteplase per kilogram of body weight to a bridging strategy of the use of alteplase (at a dose of 0.6 mg per kilogram for most of the trial) followed by endovascular therapy. The IMS-3 trial was halted for futility after 656 patients had been enrolled.[2]

Potential contributors to the neutral results of previous studies include relatively low rates of angiographic reperfusion, delays in achieving reperfusion, and the lack of patient selection with the use of advanced imaging to ensure the presence of vessel occlusion and salvageable brain tissue. None of the previous studies raised any safety concerns, with rates of symptomatic hemorrhage of approximately 6% in both the alteplase group and the endovascular-therapy group. More recent advances in device technology have significantly improved the speed and efficacy of recanalization.[5-7]

Computed tomographic (CT) perfusion imaging can indicate the extent of irreversibly injured brain in the ischemic core and potentially salvageable but hypoperfused ischemic penumbra.[8-11] Furthermore, CT perfusion imaging has evolved, and fully automated, standardized volumetric processing can now be rapidly performed in the context of a multicenter clinical trial.[12,13]

In the Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND-IA) trial, we sought to test the hypothesis that patients with anterior circulation ischemic stroke who are selected with a dual target of vessel occlusion and evidence of salvageable tissue on perfusion imaging within 4.5 hours after the onset of stroke will have improved reperfusion and early neurologic improvement when treated with early endovascular thrombectomy with the use of the Solitaire FR (Flow Restoration) stent retriever after intravenous administration of alteplase, as compared with the use of alteplase alone. The release of the MR CLEAN trial results prompted the data and safety monitoring board for our study to review the data, and the trial was stopped early because efficacy was clearly shown.

Methods

Trial Design and Oversight

The EXTEND-IA trial was an investigator-initiated, multicenter, prospective, randomized, open-label, blinded-end-point study involving patients with ischemic stroke who were receiving intravenous alteplase within 4.5 hours after stroke onset. Details of the methods used in the trial have been published previously.[14] The study protocol is available with the full text of this article at NEJM.org.

The design, analysis, and data collection for the trial were performed by members of the executive committee and investigators at the study sites (see the Supplementary Appendix, available at NEJM.org). The first author wrote the first draft of the manuscript. All the investigators vouch for the accuracy and completeness of the presented data and fidelity of the report to the study protocol. Covidien supplied the Solitaire FR device and an unrestricted grant to support trial infrastructure, but the company was not involved in the study design or conduct or in the preparation of the manuscript, except to review the protocol to ensure that the specified use of devices in the study followed the approved instructions for use.

Study Patients

We planned to enroll 100 patients at 14 centers in Australia and New Zealand. Patients were eligible if they could receive intravenous alteplase within 4.5 hours after the onset of anterior circulation ischemic stroke and had occlusion of the internal carotid artery or of the first or second segment of the middle cerebral artery, as seen on CT angiography. In addition, CT perfusion imaging, which was processed with the use of fully automated software (RAPID, noncommercial research version, Stanford University),[12,13] was used to identify potentially salvageable brain tissue. Brain tissue at risk for infarction ("ischemic penumbra") was distinguished from minimally hypoperfused tissue if the time to maximum (Tmax) delay was more than 6 seconds.[15] Irreversibly injured brain ("ischemic core") was diagnosed if the relative

cerebral blood flow was less than 30% of that in normal tissue.[10]

Endovascular therapy had to be initiated (groin puncture) within 6 hours after stroke onset and completed within 8 hours after onset. There were no restrictions on age or clinical severity, as assessed according to the score on the National Institutes of Health Stroke Scale (NIHSS), which ranges from 0 (normal) to 42 (death). However, patients were required to have functional independence before the stroke episode, which was defined as a score of less than 2 on the modified Rankin Scale, which ranges from 0 (normal) to 6 (death).

The study was approved by the institutional ethics committee at each study site. Written informed consent was obtained from patients or a legal representative before enrollment. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.

STUDY TREATMENTS

All patients received alteplase at a dose of 0.9 mg per kilogram as standard care. Patients were randomly assigned in a 1:1 ratio to receive either alteplase plus endovascular therapy (endovascular-therapy group) or no further therapy (alteplase-only group) by means of a centralized website and stratified according to the site of arterial occlusion: the internal carotid artery or the first or second segment of the middle cerebral artery.

The use of conscious sedation or general anesthesia for endovascular treatment was at the discretion of the neurointerventionist. The site of vessel occlusion was confirmed with the use of digital subtraction angiography. If there was no lesion amenable to thrombectomy, the procedure was terminated. The Solitaire FR retrievable stent (Covidien) was deployed at the site of intracranial-vessel occlusion and then removed under negative-pressure aspiration. Control angiography was performed at the conclusion of the procedure and centrally graded for angiographic revascularization, with the use of the modified Treatment in Cerebral Ischemia classification, on a scale ranging from 0 (no flow) to 3 (normal flow),[16] and any embolization of thrombus into previously uninvolved vascular territories.

STUDY OUTCOMES

The coprimary outcomes were reperfusion (which was defined as the percentage reduction in the perfusion-lesion volume between initial imaging and imaging at 24 hours, which can be negative if hypoperfusion worsens) and early neurologic improvement (which was defined as a reduction of 8 points or more on the NIHSS or a score of 0 or 1 at 3 days). Secondary outcomes were the score on the modified Rankin scale at 90 days, death due to any cause, and symptomatic intracranial hemorrhage, including any subarachnoid hemorrhage associated with clinical symptoms and symptomatic intracerebral hemorrhage, which was defined as parenchymal hematoma type 2 within 36 hours after treatment combined with an increase on the NIHSS of at least 4 points from baseline.[17] Further details are provided in the Methods section in the Supplementary Appendix.

STATISTICAL ANALYSIS

After the release of the results of the MR CLEAN study, recruitment into the trial was suspended on October 31, 2014, and the data and safety monitoring board reviewed data for the 70 enrolled patients. A prespecified Haybittle–Peto stopping boundary was applied to the coprimary outcome in the intention-to-treat population with the use of Holm's step-down procedure,[18] so that one coprimary outcome was tested at a z value of more than 3.29 and the other at a z value of more than 3. The data and safety monitoring board stopped the trial for efficacy after this analysis.

For the intention-to-treat analysis of the coprimary outcome, we compared the median percentage reperfusion between the endovascular-therapy group and the alteplase-only group after adjustment for baseline arterial occlusion strata using the van Elteren test, a stratified version of the Wilcoxon rank-sum test. We used logistic regression to compare the between-group difference in the proportion of patients with early neurologic recovery, as indicated by a reduction of 8 or more points on the NIHSS or a score of 0 or 1 at 3 days, after adjustment for age and baseline NIHSS score.

Although results are reported with and without adjustment for baseline covariates, the analysis with adjustment was prespecified as the primary analysis. The results are also reported for the target group who underwent endovascular thrombectomy according to the protocol, as compared with the alteplase-only group, to adjust for effects such as recanalization before cerebral angiography was performed and any off-protocol interventions.

As prespecified in the protocol, the initial analysis of the secondary outcome for the score on the modified Rankin scale was designed to be an assumption-free ordinal analysis[19,20] that uses the Wilcoxon–Mann–Whitney generalized odds ratio across the full range of the modified Rankin scale (from 0 to 6). Then, we used a logistic-regression model to compare the proportions of patients with scores of 0 or 1 (defined as an excellent outcome) and those with scores of 0 to 2 (defined as a functionally independent outcome) in the two study groups after adjustment for age and baseline NIHSS score.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Alteplase-Only Group (N=35)	Endovascular-Therapy Group (N=35)
Age — yr	70.2±11.8	68.6±12.3
Male sex — no. (%)	17 (49)	17 (49)
Median NIHSS score (IQR)†	13 (9–19)	17 (13–20)
Clinical history — no. (%)		
Atrial fibrillation	11 (31)	12 (34)
Hypertension	23 (66)	21 (60)
Diabetes	8 (23)	2 (6)
Smoking	15 (43)	12 (34)
Serum glucose — mmol/liter	7.6±3.6	7.1±2.5
Cause of stroke — no. (%)		
Cardioembolic occlusion	14 (40)	23 (66)
Large-artery occlusion	13 (37)	7 (20)
Undetermined or other	8 (23)	5 (14)
Median time from stroke onset to hospital arrival (IQR) — min	80 (56–115)	78 (54–112)
Median time from stroke onset to initiation of alteplase (IQR) — min	145 (105–180)	127 (93–162)
Site of vessel occlusion — no. (%)		
Internal carotid artery	11 (31)	11 (31)
Middle cerebral artery		
First segment	18 (51)	20 (57)
Second segment	6 (17)	4 (11)
Ischemic core volume at initial imaging — ml‡		
Mean	19.6±17.4	18.9±18.5
Median (IQR)	18 (4–29)	12 (4–32)
Perfusion-lesion volume at initial imaging — ml§		
Mean	116±48	105±39
Median (IQR)	115 (72–158)	106 (76–137)

* Plus–minus values are means ±SD. There were no significant differences between the two groups. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. IQR denotes interquartile range.
† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (normal) to 42 (death), with lower scores indicating less severe stroke.
‡ Irreversibly injured brain (ischemic core) was defined as cerebral blood flow of less than 30% of that in normal tissue.
§ To identify brain tissue at risk for infarction, a perfusion lesion was defined as one with a time to maximum (Tmax) delay of more than 6 seconds on computed tomographic perfusion imaging.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From August 2012 through October 2014, a total of 70 patients underwent randomization (35 to the endovascular-therapy group and 35 to the alteplase-only group) at 10 study centers (9 in Australia and 1 in New Zealand) (Fig. S1 in the Supplementary Appendix). Baseline characteristics of the patients are provided in Table 1, and procedural characteristics in Table 2.

Approximately 25% of clinically eligible patients with vessel occlusion were excluded on the basis of perfusion-imaging criteria (Fig. S2 in the Supplementary Appendix). The majority of the thrombus had been lysed before angiography in 4 of 35 patients (11%) in the endovascular-therapy group. Four other patients in the endovascular-therapy group did not undergo thrombectomy because they had either major clinical deterioration or major clinical improvement, stenting of the extracranial internal carotid artery to obtain access achieved a flow with a rating of 2b on the modified Treatment in Cerebral Ischemia classification without requiring thrombectomy, or the procedure was terminated before deployment of the Solitaire FR stent retriever owing to vessel perforation caused by microcatheter manipulation.

EFFICACY

Patients in the endovascular-therapy group had significant improvements in both coprimary end points, as compared with the alteplase-only group (Table 3). Endovascular therapy resulted in increased reperfusion at 24 hours (P<0.001) (Fig. 1A) and a probability of reperfusion of more than 90% without symptomatic intracerebral hemorrhage, as compared with the alteplase-only group (89% vs. 34%, P<0.001). The improvement in reperfusion remained highly significant in a sensitivity analysis in which 100% reperfusion was imputed for the three patients in the alteplase-

only group who had missing data owing to poor clinical status.

Endovascular therapy led to greater early neurologic recovery at 3 days (P=0.002) (Fig. 1B) and improved functional outcome in an ordinal analysis of the score on the modified Rankin scale at 90 days (generalized odds ratio, 2.0; 95% confidence interval [CI], 1.2 to 3.8; P=0.006) (Fig. 2). We determined that 2.8 patients would need to be treated with endovascular therapy to achieve improvement of at least 1 point on the functional score, as compared with the use of alteplase alone. Patients in the endovascular-therapy group were also more likely to be independent (functional score, 0 to 2) at day 90 (71% vs. 40%, P=0.01); we determined that 3.2 patients would need to be treated to achieve an independent outcome, as compared with alteplase alone. The median number of days spent at home (as compared with in the hospital or other inpatient facility) in the first 90 days after stroke[22] was 64 days greater in the endovascular-therapy group than in the alteplase-only group (P=0.001).

Consistent results were seen across the range of tertiary clinical and imaging end points (Table 3, and Table S3 in the Supplementary Appendix) and the target-group analysis (Table S5 in the Supplementary Appendix). Patients with reperfusion of 90% or more in the affected vascular territory, as compared with those with reperfusion of less than 90%, had improved functional outcome on the ordinal modified Rankin scale at 90 days (generalized odds ratio, 4.5; 95% CI, 2.2 to 9.0; P<0.001) and had increased independence (score, 0 to 2; 72% vs. 30%; P<0.001) and an excellent outcome (score of 0 or 1, 58% vs. 11%; P<0.001).

Table 2. Characteristics of Endovascular Procedures.*

Characteristic	Value
Median time from stroke onset to groin puncture (IQR) — min	210 (166–251)
Median time from hospital arrival to groin puncture (IQR) — min	113 (83–159)
Median time from initial imaging to groin puncture (IQR) — min	93 (71–138)
Median time from initiation of alteplase to groin puncture (IQR) — min	74 (54–97)
Median time from groin puncture to mTICI 2b or 3 or completion of procedure (IQR) — min	43 (24–53)
Median time from stroke onset to mTICI 2b or 3 or completion of procedure (IQR) — min	248 (204–277)
Proportion of patients receiving general anesthesia — no./total no. (%)	12/33 (36)
Final score on mTICI — no./total no. (%)†	
3	14/29 (48)
2b	11/29 (38)
2a	2/29 (7)
1	1/29 (3)
0	1/29 (3)

* The abbreviation mTICI denotes modified Treatment in Cerebral Ischemia classification, with scores ranging from 0 (no flow) to 3 (normal flow). None of the patients who had angiographic reperfusion at the end of the procedure had reocclusion on imaging at 24 hours. Further details are provided in Table S2 in the Supplementary Appendix.

† The final score was measured in the 29 patients who had an initial occlusion on angiography.

SAFETY

Symptomatic intracerebral hemorrhage occurred in two patients in the alteplase-only group (both with fatal results) and in none of the patients in the endovascular-therapy group. However, a large parenchymal hematoma developed in two patients in the endovascular-therapy group without causing major clinical deterioration; in one patient, the bleeding was caused by perforation by a wire during angiography and before deployment of the Solitaire FR stent retriever. Both patients survived, with scores of 3 and 4 on the modified Rankin scale at day 90. Embolization into a different vascular territory occurred in 2 of 35 patients (6%) in the endovascular-therapy group but did not cause clinical symptoms. There was no significant difference in mortality between the two groups, although two of the three patients in the endovascular-therapy group who died had a deterioration in their condition during the initial alteplase infusion before angiography because of a second cerebral embolism. The other adverse procedural event was a groin hematoma requiring transfusion in the endovascular-therapy group. Details regarding adverse events are provided in Table S4 in the Supplementary Appendix.

DISCUSSION

In patients with acute ischemic stroke with major vessel occlusion and salvageable tissue on CT perfusion imaging, early mechanical thrombectomy with the Solitaire FR stent retriever after the intravenous administration of alteplase was associated with faster and more complete reperfusion than the use of alteplase alone. The increase in reperfusion led to a reduction in infarct growth

Table 3. Study Outcomes.*

Outcome	Alteplase-Only Group (N=35)	Endovascular-Therapy Group (N=35)	Effect Size (95% CI)†			
			Adjusted	P Value	Unadjusted	P Value
Primary outcomes						
Median reperfusion at 24 hr (IQR) — (%)‡	37 (–0.5 to 96)	100 (100 to 100)	4.7 (2.5 to 9.0)	<0.001	4.9 (2.5 to 9.5)	<0.001
Early neurologic improvement — no. (%)§	13 (37)	28 (80)	6.0 (2.0 to 18.0)	0.002	6.8 (2.3 to 20)	<0.001
Secondary outcomes						
Score on the modified Rankin scale at 90 days¶						
Median score (IQR) on ordinal analysis	3 (1 to 5)	1 (0 to 3)	2.0	0.02	2.1 (1.2 to 3.8)	0.006
Independent outcome — no. (%)	14 (40)	25 (71)	4.2 (1.4 to 12)	0.01	3.8 (1.4 to 10.0)	0.009
Excellent outcome — no. (%)	10 (29)	18 (51)	2.4 (0.87 to 6.6)	0.09	2.6 (1.0 to 7.1)	0.05
Safety — no. (%)						
Death	7 (20)	3 (9)	0.45 (0.1 to 2.1)	0.31	0.38 (0.1 to 1.6)	0.18
Symptomatic intracerebral hemorrhage‖	2 (6)	0	NA	NA	–6 (–13 to 2)**	0.49
Parenchymal hematoma	3 (9)	4 (11)	NA	NA	3 (–11 to 17)**	0.99
Tertiary outcomes††						
Reperfusion of >90% at 24 hr without symptomatic intracerebral hemorrhage — no. (%)	12 (34)	31 (89)	27.0 (5.5 to 135.0)	<0.001	15.0 (4.0 to 52.0)	<0.001
Recanalization at 24 hr — no. (%)‡‡	15 (43)	33 (94)	29.0 (5.4 to 155.0)	<0.001	22.0 (4.5 to 106.0)	<0.001
Median infarct growth at 24 hr (IQR) — ml§§	35.3 (6.3 to 73.4)	10.9 (0 to 23.6)	–0.44 (–0.76 to –0.13)‖‖	0.007	NA	NA
Median home time (IQR) — days¶¶	15 (0 to 69)	73 (47 to 86)	64 (28 to 90)‖‖	0.001	58 (17 to 90)‖‖	0.006

* NA denotes not applicable.
† Values are odds ratios unless otherwise indicated. Odds ratios or median differences are for the endovascular-therapy group as compared with the alteplase-only group.
‡ Reperfusion was defined as the percentage reduction in the perfusion-lesion volume between initial imaging and 24-hour imaging. This value can be negative if hypoperfusion becomes more severe over time. This analysis was adjusted for the site of vessel occlusion at baseline. The effect size in this category is the Wilcoxon–Mann–Whitney generalized odds ratio.
§ Early neurologic improvement was defined as a reduction of 8 points or more on the National Institutes of Health Stroke Scale (NIHSS) or a score of 0 or 1 at 3 days. This analysis was adjusted for the NIHSS score and age at baseline.
¶ The initial analysis of the modified Rankin scale was an ordinal analysis that used the full range of the scale from 0 (normal function) to 6 (death) and is expressed as a Wilcoxon–Mann–Whitney generalized odds ratio. The analysis was adjusted for the baseline NIHSS score (≤15 vs. >15) and age (≤70 years vs. >70 years) with the use of a permutation method to accommodate small stratum size. This method does not produce confidence intervals. In addition, scores on the modified Rankin scale were analyzed for an outcome with functional independence (score of 0 to 2) or an excellent outcome (score of 0 or 1), adjusted for the full range of ages and baseline score on the NIHSS.
‖ Symptomatic intracerebral hemorrhage was defined as a large parenchymal hematoma (blood clot occupying >30% of infarct volume with mass effect) and an increase of 4 points or more in the NIHSS score.
** The effect size in this category is a risk difference, as measured in percentage points for symptomatic intracerebral hemorrhage and parenchymal hematoma.
†† A more detailed list of tertiary outcomes is provided in Table S3 in the Supplementary Appendix.
‡‡ Recanalization was defined as a Thrombolysis in Myocardial Infarction score of 2 or 3 (partial or complete restoration of flow at the site of arterial occlusion).[21] This analysis was adjusted for the site of vessel occlusion at baseline.
§§ Infarct growth was defined as the increase in the ischemic core volume from baseline to 24 hours and was adjusted for the ischemic core volume at baseline.
¶¶ Home time (the number of days spent at home during the first 90 days after the diagnosis of stroke) was adjusted for the NIHSS score and age at baseline.
‖‖ The effect size in this category is the median difference in infarct growth (as measured in milliliters and transformed by an exponent of 0.2 owing to a non-normal distribution) and the median difference in days for home time, as calculated by median regression.

and substantial clinical benefit in early neurologic recovery and functional outcome at 3 months. This reduction in infarct growth is consistent with salvage of ischemic penumbra as the mechanism of underlying clinical benefit.[23]

The magnitude of the clinical benefit of en-

dovascular thrombectomy in our study was larger than that in previous trials, despite similar clinical severities and demographic characteristics. The results of this trial were unequivocal, despite the small sample size. Key differences between our study and the previous trials include the use of CT perfusion imaging to select patients with the greatest potential to benefit from endovascular therapy, shorter time to the onset of treatment, and improved rates of angiographic revascularization.

A unique feature of our study was the use of standardized, universal CT perfusion-imaging selection to exclude patients with large ischemic cores and without evidence of clinically significant salvageable ischemic brain. Such patients have a low probability of a good outcome and have a higher risk of symptomatic hemorrhage and malignant edema.[15,24] In the time window of less than 4.5 hours, patients with large ischemic cores comprise 10 to 15% of an unselected population,[24] a rate that was generally consistent with the estimate of 25% of patients (95% CI, 11 to 45) who were excluded from our study on the basis of perfusion-imaging criteria. Such patients may not only undergo futile reperfusion but also have a reduced treatment effect if reperfusion leads to hemorrhage or malignant edema. This factor may be particularly relevant if the intervention has a higher reperfusion rate than that in controls, which was shown in our study to be applicable to endovascular therapy. CT perfusion imaging was also performed in about 65% of patients in the MR CLEAN trial (Majoie C: personal communication). Such imaging was not required according to the protocol for the MR CLEAN trial but may have influenced patient selection. Hence, positive results in the MR CLEAN trial may not be entirely attributable to imaging selection on the basis of vessel occlusion alone.

The interval between the initiation of alteplase and randomization was 30 minutes in our study, as compared with 100 minutes in the MR CLEAN trial, because of our approach of identifying patients with the greatest potential to benefit from reperfusion and then maximizing early reperfusion with the use of combined alteplase and endovascular therapy, rather than waiting to assess clinical response to alteplase. As a result, the time from stroke onset to the initiation of the endovascular procedure was a median of 50 minutes shorter than the similar interval in the MR CLEAN trial, which may also have contributed to the substantially higher proportion of patients with independent functional outcomes observed in our study. Only 11% of the patients in our study had no retrievable thrombus on initial angiography, which is consistent with results that have been reported previously[25] and mitigates any concern regarding unnecessary angiography. As endovascular therapy becomes standard care, there is further potential to

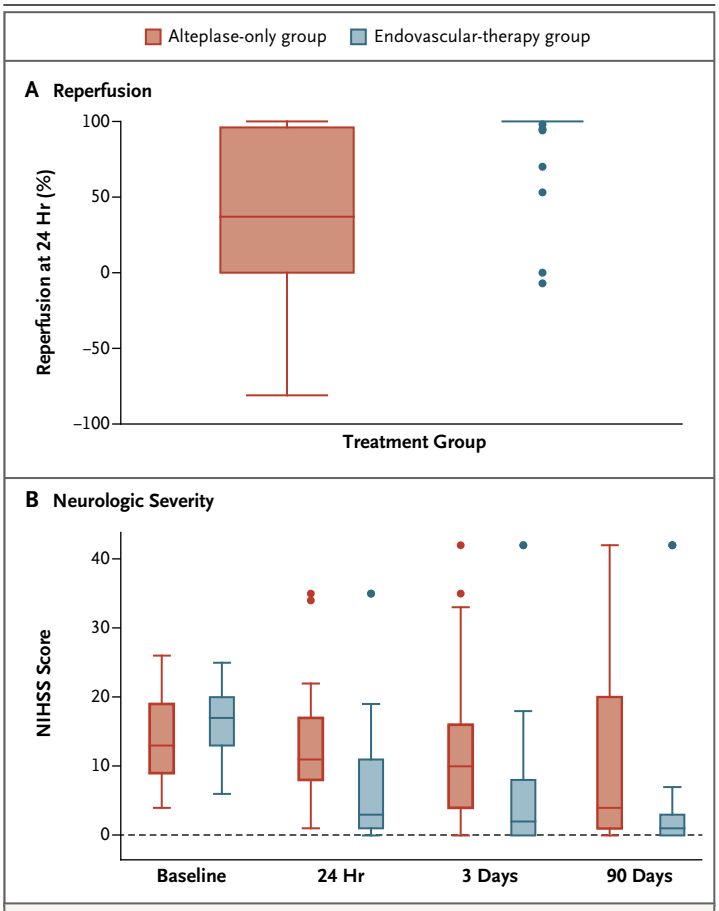

Figure 1. Reperfusion and Functional Scores.

Panel A shows box plots for the rate of reperfusion at 24 hours (the coprimary end point) among patients receiving intravenous alteplase plus endovascular therapy (endovascular-therapy group) and those receiving alteplase only (100% vs. 37%, P<0.001). The horizontal line within the box plot for the alteplase-only group represents the median, the top and bottom of each box indicate the interquartile range, I bars indicate 1.5 times the interquartile range, and the circles indicate outliers. For the endovascular-therapy group, the median was 100%, with six outliers. Panel B shows box plots for the changes in the distribution of scores on the National Institutes of Health Stroke Scale (NIHSS) from baseline to 24 hours, 3 days, and 90 days. NIHSS is a standardized neurologic examination and ranges from 0 (normal) to 42 (death), with lower scores indicating less severe stroke. There was an early and sustained reduction in NIHSS scores in the endovascular-therapy group, as compared with the alteplase-only group.

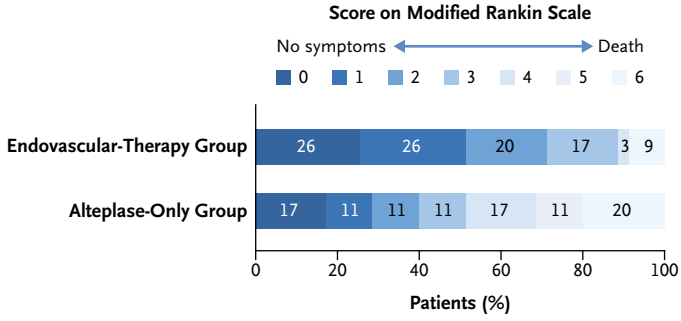

Figure 2. Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population.

Shown are the percentages of patients in the endovascular-therapy group and the alteplase-only group with scores from 0 to 6 on the modified Rankin scale as follows: 0, no symptoms; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability requiring some help (e.g., with shopping, cleaning, and finances but able to walk unassisted); 4, moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted); 5, severe disability (requiring constant nursing care and attention); and 6, death. In the endovascular group, no patients had a score of 5.

streamline the "door-to-puncture" process and perhaps achieve even greater clinical benefits.

The rate of successful revascularization immediately after the procedure (86% of patients had a restoration of flow to >50% of the stroke-affected territory) was higher in our study than in previous randomized trials but is consistent with registry studies in which the Solitaire FR stent retriever was used.[5] This finding probably relates to the use of earlier-generation devices and techniques in the IMS-3 and the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trials. The reperfusion rate in our study was also higher than the 58% reported in MR CLEAN, in which stent retrievers were used in 81.5% of patients. There is some evidence that the success of recanalization is increased in patients with good collateral flow,[26] which correlates strongly with the presence of a "mismatch" pattern on perfusion imaging between a small, irreversibly injured ischemic core and a larger perfusion lesion indicating the presence of salvageable ischemic penumbra.[27] The imaging selection of patients may therefore have chosen patients with a better chance of recanalization.

Our study, which was conducted at multiple centers with varying levels of imaging expertise, shows the practicality and generalizability of fully automated image processing. The time that is required to acquire, process, and interpret images is largely a function of computer-network speed and processing power, and should be less than 15 minutes.[12] Analysis of the CT perfusion images occurred in parallel with administration of alteplase so that there was no treatment delay.[28]

Strengths of our study include the selection of patients who were most likely to benefit from reperfusion, earlier intervention, and a standardized stent-retriever intervention with more complete revascularization. Also, the routine assessment of reperfusion at 24 hours has the advantage of being quantitative, blinded, and objective because of the automated software that was used. The 24-hour interval provides assurance that reocclusion after initial successful recanalization is uncommon in such patients. Previous studies have been restricted to assessing angiographic reperfusion rates in only the endovascular group or, in some cases, recanalization at 24 hours in a subgroup of patients.[2]

Limitations of the study include the inability to perform subgroup analyses, given the small number of patients. Such analyses will require individual patient meta-analysis of multiple trials. We cannot rule out the possibility that some of the patients who were excluded from the trial on the basis of a large ischemic core or absence of significant salvageable ischemic brain tissue might have benefited from endovascular therapy. Purely volume-based criteria do not account for the location of the core, which is also relevant to the clinical outcome.[29] The early termination of the trial does create potential for overestimation of the effect size. However, the investigators believed that the new information from the MR CLEAN trial ethically mandated review by the independent data and safety monitoring board. The details of the statistical stopping rule were highly conservative and were agreed on between investigators and the data and safety monitoring board in advance of accessing the data.

In conclusion, we found that patients with ischemic stroke with a proximal cerebral arterial occlusion and salvageable tissue on CT perfusion imaging had improved reperfusion, early neurologic recovery, and functional outcome if endovascular thrombectomy with the Solitaire FR stent retriever was performed without delay after the initiation of intravenous alteplase. Further studies

will be needed to clarify remaining uncertainties regarding the benefit in patients with more distal occlusions, later time windows, and the influence of the type of device that is used and variability in the endovascular technique.

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APPENDIX

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