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Endovascular Thrombectomy with or without Intravenous Alteplase in Acute Stroke

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ABSTRACT

BACKGROUND

In acute ischemic stroke, there is uncertainty regarding the benefit and risk of administering intravenous alteplase before endovascular thrombectomy.

METHODS

We conducted a trial at 41 academic tertiary care centers in China to evaluate endovascular thrombectomy with or without intravenous alteplase in patients with acute ischemic stroke. Patients with acute ischemic stroke from large-vessel occlusion in the anterior circulation were randomly assigned in a 1:1 ratio to undergo endovascular thrombectomy alone (thrombectomy-alone group) or endovascular thrombectomy preceded by intravenous alteplase, at a dose of 0.9 mg per kilogram of body weight, administered within 4.5 hours after symptom onset (combination-therapy group). The primary analysis for noninferiority assessed the between-group difference in the distribution of the modified Rankin scale scores (range, 0 [no symptoms] to 6 [death]) at 90 days on the basis of a lower boundary of the 95% confidence interval of the adjusted common odds ratio equal to or larger than 0.8. We assessed various secondary outcomes, including death and reperfusion of the ischemic area.

RESULTS

Of 1586 patients screened, 656 were enrolled, with 327 patients assigned to the thrombectomy-alone group and 329 assigned to the combination-therapy group. Endovascular thrombectomy alone was noninferior to combined intravenous alteplase and endovascular thrombectomy with regard to the primary outcome (adjusted common odds ratio, 1.07; 95% confidence interval, 0.81 to 1.40; P=0.04 for noninferiority) but was associated with lower percentages of patients with successful reperfusion before thrombectomy (2.4% vs. 7.0%) and overall successful reperfusion (79.4% vs. 84.5%). Mortality at 90 days was 17.7% in the thrombectomy-alone group and 18.8% in the combination-therapy group.

CONCLUSIONS

In Chinese patients with acute ischemic stroke from large-vessel occlusion, endovascular thrombectomy alone was noninferior with regard to functional outcome, within a 20% margin of confidence, to endovascular thrombectomy preceded by intravenous alteplase administered within 4.5 hours after symptom onset. (Funded by the Stroke Prevention Project of the National Health Commission of the People's Republic of China and the Wu Jieping Medical Foundation; DIRECT-MT ClinicalTrials.gov number, NCT03469206.)

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Endovascular thrombectomy has become part of the standard treatment for patients who have acute ischemic stroke due to large-vessel occlusion in the anterior cerebral circulation, when the procedure is available and can be performed in a timely fashion or is based on a mismatch between regional brain perfusion and infarction.[1-6] Endovascular treatment has been compared with intravenous administration of the thrombolytic agent alteplase. However, there is uncertainty regarding the role of alteplase before and during thrombectomy in patients with ischemic stroke. Alteplase may increase early reperfusion of the ischemic area and dissolve residual distal thrombi after endovascular thrombectomy.[7-10] For large, proximally located thrombi, however, the lytic effect of intravenous alteplase is limited, and partial lysis could fragment the target thrombus or cause it to migrate distally, potentially complicating endovascular thrombectomy.[11,12] Intravenous alteplase may also increase the risk of cerebral hemorrhage.[13] Meta-analyses of observational studies suggest equivalent effects of endovascular thrombectomy alone and thrombectomy combined with standard alteplase treatment, but data from randomized comparisons of these two strategies are limited.[14-16] We undertook the Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: a Multicenter Randomized Clinical Trial (DIRECT-MT) to determine whether endovascular thrombectomy alone would be noninferior to combined treatment with endovascular thrombectomy preceded by intravenous alteplase in patients who had acute ischemic stroke with large-vessel occlusion in the anterior circulation.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted an investigator-initiated, multicenter, prospective, randomized, open-label trial with blinded outcome assessment involving patients with acute ischemic stroke who were eligible both to receive intravenous alteplase and to undergo endovascular thrombectomy. Patients underwent randomization centrally to undergo endovascular thrombectomy alone or to receive combined treatment with intravenous alteplase (at a dose of 0.9 mg per kilogram of body weight) before endovascular thrombectomy.

The protocol, which has been published previously[17] and is available with the full text of this article at NEJM.org, was approved by all relevant local ethics committees and research boards. The final protocol and statistical analysis plan were completed on August 20, 2019, and October 21, 2019, respectively; these events occurred after the last patient had been enrolled and assessed on July 2, 2019, and September 18, 2019, respectively. At that time, the results were still blinded to investigators and to persons handling the data and performing the analysis, including those in the contract research organization. Written informed consent was obtained before enrollment from all the patients or their legal representatives. All the investigators vouch for the completeness and accuracy of the data, for the fidelity of the trial to the protocol, and for the accurate reporting of adverse events.

The trial was funded by the National Health Commission of China and the Wu Jieping Medical Foundation; these entities were not involved in the trial design, conduct, protocol review, manuscript preparation, or decision to submit the manuscript for publication. Alteplase was paid for by the patients, who later received various degrees of reimbursement from the Chinese social security system. In most instances, the patients or their families had to either agree in advance to pay for the use of alteplase or pay at the time of enrollment. Procedures were instituted in 2013, before the start of the trial, to allow patients to pay after the infusion occurred, in order to avoid delay in treatment.

A steering committee met monthly to oversee the trial. An independent data and safety monitoring board was responsible for safety, ethics, and conduct oversight with the use of results of interim analyses. An independent contract research organization (Cardiovascular Chinese Research Center, http://ccrcmed.com) and site management organization (Shanghai Taisure Medical Technology, www.taisure-med.com) were involved in monitoring to ensure trial quality (see the Supplementary Appendix, available at NEJM.org).

PATIENTS AND PARTICIPATING CENTERS

The trial was conducted at 41 academic tertiary care centers in 18 provinces in China. Sites were

selected on the basis of their stroke treatment capabilities as recorded in a national prospective database of Chinese stroke centers, which is regulated by the Stroke Prevention Project office affiliated with the National Health Commission of China (www.cnstroke.com). All the sites were required to have performed at least 30 endovascular thrombectomy procedures during the previous year. On-site and online training were provided before and during the trial period to ensure compliance with the protocol, assessments, and standard of care (Sections S2.3 through S2.6 in the Supplementary Appendix).

Patients were eligible for inclusion in the trial if they were 18 years of age or older; had an occlusion of the intracranial segment of the internal carotid artery (both terminus and nonterminus occlusions) or of the first or proximal second segment of the middle cerebral artery, or both, as shown on computed tomographic angiography (CTA), that could be treated with intravenous alteplase within 4.5 hours after symptom onset; and had a neurologic deficit as indicated by a score of at least 2 points on the National Institutes of Health Stroke Scale (NIHSS; range, 0 [no symptoms] to 42 [most severe neurologic deficits]). Information about the extent of early cerebral ischemia on baseline computed tomography (CT) as measured by the Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range, 0 to 10, with higher scores indicating fewer early ischemic changes) was not required for inclusion in the trial. Patients were excluded from the trial if they had a disability before the stroke or had any contraindication to intravenous alteplase according to the American Heart Association (AHA)–American Stroke Association (ASA) guidelines.[18] Disability before the stroke was defined as a score of more than 2 on the modified Rankin scale (range, 0 [normal] to 6 [death]) and was assessed by the treating physician with the use of information obtained from patients (if possible) or their family members. Detailed inclusion and exclusion criteria are listed in Section S2.2. A screening log of the patients who were assessed for eligibility was kept at each investigational site.

RANDOMIZATION AND BLINDING

Randomization was performed in a 1:1 ratio with the use of a Web-based system, with stratification according to participating site. The treatment-group assignment was known to both the treating physician and the patient. The members of the outcome committee and the imaging core laboratory, who determined the primary and secondary outcomes, were unaware of the treatment-group assignments. Two interim analyses were performed by an independent statistician and reported to the data and safety monitoring board but were masked to the investigators.

TRIAL TREATMENTS

Patients who had been randomly assigned to receive intravenous alteplase received the treatment according to AHA–ASA and local guidelines: a standard dose of 0.9 mg per kilogram of body weight (with 10% administered as a bolus, and 90% infused over a period of 1 hour) to a maximum of 90 mg, which was generally guided by direct measurement of body weight or in some cases was estimated. The alteplase infusion could be completed during endovascular thrombectomy, even if the procedure was successful in establishing revascularization. Patients who had been randomly assigned to undergo endovascular thrombectomy alone had no alteplase administration before or during the procedure.

The endovascular thrombectomy devices that were used in the trial had been approved by the China Food and Drug Administration. A stent retriever was the primary device; aspiration devices could be used as a secondary option if the initial reperfusion failed. Intraarterial alteplase (maximum dose, 30 mg) or urokinase (maximum dose, 400,000 U) were accepted as rescue therapy in both groups, at the discretion of the treating physician.

TRIAL OUTCOMES

The primary outcome was the score on the modified Rankin scale assessed at 90 days (within a window of ±14 days) after randomization and was analyzed for noninferiority.[19] Superiority was to be tested as a secondary objective if the primary analysis suggested that superiority was likely. Outcome data were obtained from structured interviews that were performed in person or by telephone with the use of standardized forms; interviews were conducted by local trained physicians who were unaware of the trial-group assignments. Standardized written reports of each interview were provided to two members of an

outcome committee, who verified the score by consensus.

Secondary outcomes were the following: death within 90 days; successful reperfusion before thrombectomy as assessed with the extended Thrombolysis in Cerebral Infarction (eTICI) score (range, 0 [no reperfusion] to 3 [complete reperfusion]) on the first intracranial angiogram (performed with digital subtraction angiography); an eTICI score of 2b, 2c, or 3 on the final angiogram[20]; the percentage of patients with recanalization at 24 to 72 hours as assessed by CTA; the NIHSS score at 24 hours and at 5 to 7 days (or at hospital discharge)[21]; the final lesion volume on CT conducted without the use of contrast material; comparisons of modified Rankin scale scores (0 or 1 vs. 2 to 6; 0 to 2 vs. 3 to 6; 0 to 3 vs. 4 to 6; 0 to 4 vs. 5 or 6; and 0 to 5 vs. 6) at 90 days; the score on the EuroQoL Group 5-Dimension 5-Level Self-Report questionnaire on health-related quality of life (range, −0.39 [worst] to 1.00 [best]); and the Barthel Index score (range, 0 [severe disability] to 100 [no disability]) at 90 days.[22,23] Safety outcomes were all hemorrhages and symptomatic intracranial hemorrhages according to the Heidelberg criteria,[24] embolization in new cerebrovascular territory, the occurrence of pseudoaneurysm and groin hematoma at the site of arterial puncture used for thrombectomy, cerebral infarction in a new vascular territory at 5 to 7 days, and mortality within 90 days.

Clinical assessments were performed at baseline, at 24 hours after randomization, at 5 to 7 days or at the time of hospital discharge (whichever came first), and at 90 days (within a window of ±14 days). All the clinician assessors received both on-site and Web-based video training on how to perform the clinical assessments. Imaging was evaluated at an independent imaging core laboratory by trained staff who were unaware of the treatment assignments. All the images were read by two readers, with consensus reached in case of discrepancies (Sections S2.7 and S2.8). The final lesion volume was assessed by an automated, validated computer algorithm.[1,25]

STATISTICAL ANALYSIS

We estimated that a sample size of 636, determined by running 5000 Monte Carlo simulations, would provide the trial with 80% power (at a two-sided alpha level of 0.05) to determine a noninferiority margin of 0.8, assuming a common odds ratio for scores on the modified Rankin scale of 1.16. This effect would correspond to a difference of 4 percentage points between the patients in the thrombectomy-alone group in our trial who had a modified Rankin scale score in the 0-to-2 range and the intervention group in the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) trial.[1] We also assumed that there would be 5% withdrawal and a conservative 15% reduction in the sample size because of adjustment for major prognostic variables that included age, baseline stroke severity (according to the NIHSS score), the modified Rankin scale score before stroke onset, cerebral collateral blood-flow status, and the time from stroke onset to randomization.[26,27] A total of 20 additional patients were enrolled in order to compensate for those who had major protocol violations.

Baseline data are presented according to treatment assignment, with descriptive statistics as appropriate. Missing data for baseline characteristics were imputed with the use of multiple imputation by fully conditional specification regression for continuous variables or by fully conditional specification logistic regression for binary and ordinal variables. All the analyses for the primary, secondary, and safety outcomes were performed according to the intention-to-treat principle, except that patients who were lost to follow-up would not be included in the primary outcome analysis.

The primary effect was determined as a common odds ratio with adjustment for major prognostic variables and estimated by ordinal logistic regression. Estimates with corresponding 95% confidence intervals, with adjustment for age, baseline stroke severity (NIHSS score), the modified Rankin scale score before stroke onset, cerebral collateral blood-flow status, and the time from stroke onset to randomization, are reported.

Secondary outcomes were analyzed by linear- or logistic-regression analyses, as appropriate, with the same adjustments as used for the primary outcome. Because there was no plan for adjustment for multiple comparisons of secondary outcomes, these results are presented as point estimates with multiplicity-unadjusted confidence intervals, from which no clinical inferences can

be made. The primary outcome was also assessed in a per-protocol population that consisted of patients who met all the eligibility criteria and received the assigned treatment or had recovered or had deterioration in their condition before receiving endovascular treatment.

All the analyses were performed with the use of SAS software, version 9.2 (SAS Institute). Figures were drawn with the use of R software, version 3.3.3 (R Development Core Team 2017, www.r-project.org).

RESULTS

PATIENTS

From February 23, 2018, through July 2, 2019, a total of 1586 patients were assessed for eligibility at 41 sites; a total of 656 patients were enrolled (Fig. 1 and Fig. S3 and Table S1 in the Supplementary Appendix). A total of 327 patients were assigned to undergo endovascular thrombectomy alone (thrombectomy-alone group) and 329 were assigned to receive combination therapy with intravenous alteplase and endovascular thrombectomy (combination-therapy group).

The baseline characteristics of the patients were similar in the treatment groups (Table 1 and Table S2). The median age of the patients was 69 years (interquartile range, 61 to 76), and 370 patients (56.4%) were men. Among patients with available data, the median NIHSS score was 17 (interquartile range, 13 to 22), and the median ASPECTS value was 9 (interquartile range, 7 to 10). The median time from stroke onset to randomization was 167 minutes (interquartile range, 125 to 206) in the thrombectomy-alone group and 177 minutes (interquartile range, 126 to 215) in the combination-therapy group; the median time from randomization to groin puncture was 31 minutes (interquartile range, 20 to 45) and 36 minutes (interquartile range, 22 to 50.5), respectively.

INTERVENTIONS

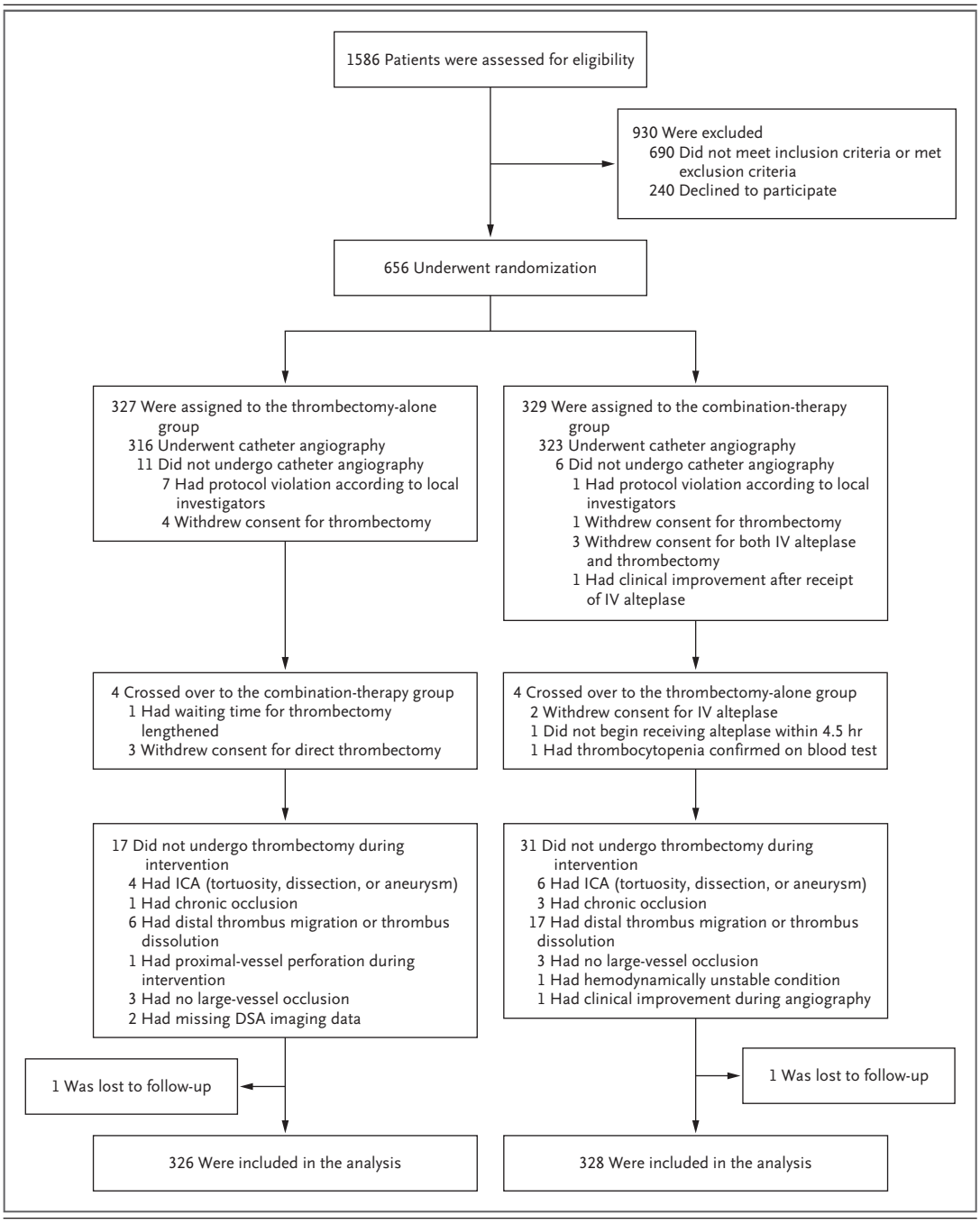
A total of 639 patients underwent groin puncture; of these, 591 underwent endovascular thrombectomy, which was defined as coming in contact with the thrombus by means of any intraarterial device (299 patients [91.4%] in the thrombectomy-alone group and 292 patients [88.8%] in the combination-therapy group) (Fig. 1). Stent retrievers were used in 566 of 591 patients (95.8%) (Table S3). There were 25 major protocol violations, which involved 17 patients who did not receive any groin puncture and 4 patients in each group who crossed over to the alternative treatment. In the combination-therapy group, 319 of 329 patients (97.0%) received alteplase, of whom 23 completed the infusion before groin puncture and 276 (86.5% of those who received alteplase) completed the infusion during the endovascular procedure (Table S4). A total of 14 patients (7 in each group) underwent intraarterial thrombolysis. General anesthesia was used in 207 of the 639 patients (32.4%) who underwent endovascular thrombectomy, in similar proportions in each group (33.2% in the thrombectomy-alone group and 31.6% in the combination-therapy group). A total of 45 patients (6.9%) were judged by the imaging core laboratory to have intracranial atherosclerotic disease related to large-vessel occlusion.

PRIMARY OUTCOME

The primary outcome of the modified Rankin scale score at 90 days was missing for 2 patients (1 patient in each group), and data were not imputed. The adjusted common odds ratio for the modified Rankin scale score at 90 days was 1.07 (95% confidence interval [CI], 0.81 to 1.40; P=0.04) (Fig. 2). Thrombectomy alone was noninferior to combination thrombectomy with intravenous alteplase treatment because the lower boundary of the confidence interval was greater than the prespecified value of 0.8 (unadjusted common odds ratio, 1.09; 95% CI, 0.84 to 1.43; P=0.02). The per-protocol analysis yielded similar results (Table S6). Because the lower boundary of the confidence interval was just above the prespecified boundary for noninferiority, testing for superiority was not formally analyzed. Prespecified subgroup analyses are shown in Figure S4.

SECONDARY OUTCOMES

Mortality at 90 days was 17.7% in the thrombectomy-alone group and 18.8% in the combination-therapy group. The percentage of patients with successful reperfusion (eTICI score, ≥2b) before thrombectomy was 2.4% in the thrombectomy-alone group and 7.0% in the combination-therapy group, and successful reperfusion on final angiography was observed in 79.4% and 84.5%, respectively. Other secondary outcomes are shown in Table 2. For all nine clinical secondary outcomes and for three of the four imag-



ing secondary outcomes, the confidence intervals for the odds ratios included 1 or those for the beta coefficients included 0; however, no conclusions can be made regarding differences for secondary outcomes because of the lack of planned adjustment of confidence intervals for multiple comparisons.

SAFETY

The percentages of patients with serious adverse events during the 90-day follow-up period were similar in the two groups (37.0% [121 of 327 patients] in the thrombectomy-alone group and 36.8% [121 of 329] in the combination-therapy group). The percentages of patients with intra-

Figure 1 (facing page). Randomization and Treatment of the Patients.

Patients were randomly assigned in a 1:1 ratio to undergo endovascular thrombectomy (thrombectomy-alone group) or to receive intravenous (IV) alteplase followed by endovascular thrombectomy (combination-therapy group). Endovascular thrombectomy was defined as coming into contact with the thrombus by any device. Crossover from the combination-therapy group to the thrombectomy-alone group was defined as patients who did not receive intravenous alteplase but who underwent thrombectomy. Six additional patients who did not receive intravenous alteplase were not defined as having crossed over because five of them did not receive endovascular thrombectomy and one received intravenous urokinase. Chronic occlusion was judged by the treating physician according to imaging characteristics and clinical symptoms after catheter angiography; endovascular thrombectomy was not attempted in these patients. Thrombus dissolution was defined as recanalization of the occluded artery and complete reperfusion of the target ischemic territory, which indicated the thrombus was totally dissolved. Digital subtraction angiographic (DSA) imaging data were lost for two patients owing to a computer virus; the imaging core laboratory could not evaluate the procedural details. ICA denotes internal carotid artery.

cranial hemorrhages — both symptomatic (4.3% [14 patients] in the thrombectomy-alone group and 6.1% [20 patients] in the combination-therapy group) and asymptomatic (33.3% [109 patients] and 36.2% [119 patients], respectively) — did not differ significantly between the groups. Procedural complications occurred in 49 patients (15.0%) in the thrombectomy-alone group and in 47 (14.3%) in the combination-therapy group (Table 3).

DISCUSSION

In patients with acute ischemic stroke due to large-vessel occlusion in the anterior circulation who were eligible for treatment with both intravenous alteplase and endovascular thrombectomy according to most guidelines, direct intervention with intraarterial thrombectomy was noninferior to the combination of initial intravenous alteplase followed by endovascular thrombectomy. Because the lower boundary of the 95% confidence interval for the common odds ratio comparing the modified Rankin scale scores at 90 days was just above the prespecified value of 0.8 in the unadjusted and adjusted analyses, the results do not rule out a benefit of alteplase.

Given the potential risk of hemorrhage and the cost of intravenous alteplase, investigators have questioned the need for intravenous thrombolysis if patients are eligible to undergo endovascular thrombectomy and the procedure can be performed in a timely fashion.[13,28] Previous observational studies that had been aimed at resolving this issue had selection bias, such as the inclusion of patients who were eligible to receive alteplase as well as those who were not eligible, and incomplete adjustment for confounding factors.[15,16,29,30] The results of our trial are consistent with findings from a meta-analysis that attempted to eliminate bias and confounding,[16] but our results contrast with those of other meta-analyses that did not perform adjustment procedures and that showed the superiority of the combined treatment.[29,30]

The percentages of patients with functional independence in our trial are similar to those reported in the intervention group of the MR CLEAN trial,[1] which used patient-selection criteria that were similar to those in our trial. Although no overall beneficial effect of alteplase was analyzed in our trial, a higher percentage of patients with successful reperfusion before thrombectomy, as assessed on digital subtraction angiography, was observed in the group receiving intravenous alteplase with endovascular therapy than in the group that underwent thrombectomy alone; however, the lack of a plan for multiple comparisons of secondary outcomes means that inferences cannot be made from these results. The proportion of patients with early reperfusion in our trial was also similar to that reported in the control group of the Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial, but it was lower than that reported in the tenecteplase group of that trial.[31] Pretreatment with alteplase in our trial resulted in a delay of only 5 minutes in the time from randomization to groin puncture, but this delay may have been accounted for in part by continuing the alteplase infusion during the endovascular procedure in 86.5% of the patients. The incomplete infusion before the procedure may have obscured the effects of intravenous alteplase in the group receiving combined therapy and influenced the trial results. This differ-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Endovascular Thrombectomy (N=327)	Alteplase with Endovascular Thrombectomy (N=329)
Median age (IQR) — yr	69 (61–76)	69 (61–76)
Male sex — no. (%)	189 (57.8)	181 (55.0)
Median NIHSS score (IQR)†	17 (12–21)	17 (14–22)
Medical history — no. (%)		
Previous ischemic stroke	43 (13.1)	47 (14.3)
History of atrial fibrillation	152 (46.5)	149 (45.3)
History of diabetes mellitus	59 (18.0)	65 (19.8)
History of hypertension	193 (59.0)	201 (61.1)
Modified Rankin scale score of 1 or 2 before stroke onset — no. (%)‡	27 (8.3)	24 (7.3)
Median ASPECTS (IQR)§	9 (7–10)	9 (7–10)
Median systolic blood pressure at hospital arrival (IQR) — mm Hg	146 (130–163)	146 (131–161)
Median glucose level at hospital arrival (IQR) — mmol/liter¶	7.0 (5.8–8.6)	7.0 (5.9–8.8)
Cause of stroke — no. (%)‖		
Cardioembolism	146 (44.6)	144 (43.8)
Intracranial atherosclerosis	26 (8.0)	19 (5.8)
Ipsilateral extracranial ICA obstruction	34 (10.4)	29 (8.8)
Undetermined	121 (37.0)	137 (41.6)
Median duration (IQR) — min		
From stroke onset to randomization	167 (125–206)	177 (126–215)
From randomization to start of alteplase**	NA	7 (4–12)
From randomization to groin puncture††	31 (20–45)	36 (22–50.5)
From randomization to revascularization‡‡	102 (74–141)	96 (71.5–130.5)
From hospital admission to intravenous alteplase§§	NA	59 (45–78)
From hospital admission to groin puncture¶¶	84 (67–105)	85.5 (70–115)
Location of intracranial artery occlusion — no./total no. (%)‖‖		
Intracranial ICA	112/320 (35.0)	114/326 (35.0)
M1 middle cerebral artery segment	161/320 (50.3)	178/326 (54.6)
M2 middle cerebral artery segment	42/320 (13.1)	33/326 (10.1)

* ICA denotes internal carotid artery, IQR interquartile range, and NA not applicable.

† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits. Data were missing for 3 patients (2 in the thrombectomy-alone group and 1 in the combination-therapy group).

‡ Scores on the modified Rankin scale of functional recovery range from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence. The modified Rankin scale score before stroke onset was assessed by the treating physician with the use of information obtained from patients (if possible) or their family members. Only patients with a modified Rankin scale score of 0 to 2 were included in the trial.

§ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is a measure of the extent of early cerebral ischemia. Scores ranges from 0 to 10, with higher scores indicating fewer early ischemic changes. Shown are values as assessed by the core laboratory. Scores were not available for 4 patients in the thrombectomy-alone group and for 3 in the combination-therapy group.

¶ Data were missing for 2 patients in the thrombectomy-alone group and for 5 in the combination-therapy group. To convert the values for glucose to milligrams per deciliter, divide by 0.05551.

Table 1. (Continued.)

‖ The cause of stroke was assessed according to the medical history, clinical features, and results on digital subtraction angiography.

** For the time from randomization to the start of alteplase administration, 319 patients in the combination-therapy group were included in the analysis. A total of 10 patients did not receive intravenous alteplase owing to crossover (4 patients), withdrawal of consent (4), and protocol violation (2).

†† For the time from randomization to groin puncture, 636 patients were included in the analysis. Data were missing for 3 patients (2 in the thrombectomy-alone group and 1 in the combination-therapy group). A total of 17 patients did not undergo catheter angiography.

‡‡ For the time from randomization to revascularization, 636 patients were included in the analysis. Revascularization was defined as the first visualization of successful reperfusion, as indicated by an extended Thrombolysis in Cerebral Infarction (eTICI) score of 2b, 2c, or 3 (on a scale from 0 [no reperfusion] to 3 [complete reperfusion]). For patients who underwent angiography only or had unsuccessful revascularization, the time of the last bolus of contrast material was considered to be the time to revascularization. These patients were included in the analysis because procedures times are typically longer in patients with unsuccessful revascularization than in those with successful revascularization.

§§ Data on the time from hospital admission to the administration of intravenous alteplase were missing for 27 patients and were imputed by multiple-regression interpolation.

¶¶ Data on the time from hospital admission to groin puncture were missing for 35 patients (16 in the thrombectomy-alone group and 19 in the combination-therapy group) and were imputed by multiple-regression interpolation.

‖‖ The sites of intracranial artery occlusion were assessed by the core laboratory. Computed tomographic angiographic data at baseline were missing for 10 patients (7 in the thrombectomy-alone group and 3 in the combination-therapy group). A total of 6 patients (5 in the thrombectomy-alone group and 1 in the combination-therapy group) did not have a target artery occlusion, including 1 patient with anterior cerebral artery occlusion, 2 with severe stenosis, and 3 without proximal large-vessel occlusion.

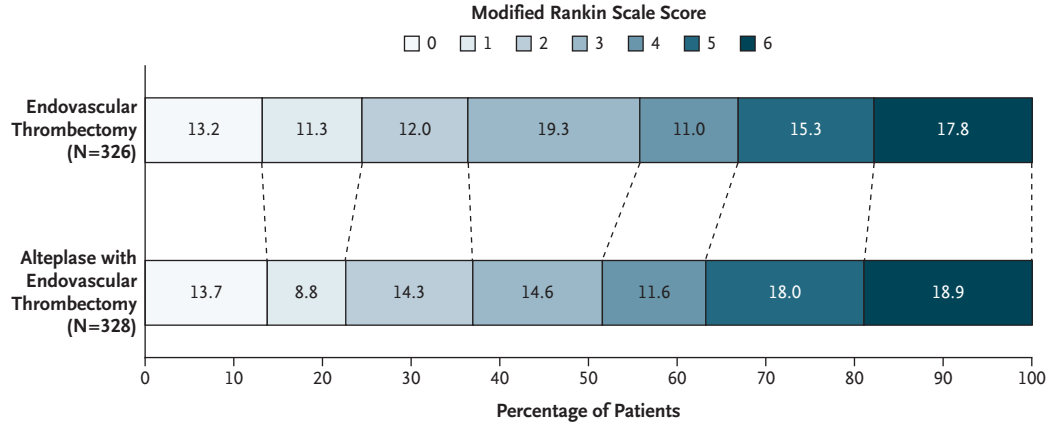


Figure 2. Distribution of Functional Outcomes at 90 Days in the Intention-to-Treat Population.

Shown are scores on the modified Rankin scale for the patients in the two treatment groups who had data for the primary outcome; two patients were lost to follow-up, and data were not imputed. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability (patients are able to look after their own affairs without assistance but are unable to carry out all previous activities), 3 moderate disability (patients require some help but are able to walk unassisted), 4 moderately severe disability (patients are unable to attend to bodily needs without assistance and are unable to walk unassisted), 5 severe disability (patients require constant nursing care and attention), and 6 death. Endovascular thrombectomy alone was noninferior to alteplase with endovascular thrombectomy in the univariable ordinal regression analysis that used a margin of 0.8 (common odds ratio, 1.09; 95% CI, 0.84 to 1.43), as well as after adjustment for age, the National Institutes of Health Stroke Scale score at baseline, the time from stroke onset to randomization, the modified Rankin scale score before stroke onset, and the cerebral collateral blood-flow status in an analysis with multivariable ordinal regression that used a margin of 0.8 (adjusted common odds ratio, 1.07; 95% CI, 0.81 to 1.40). Percentages may not total 100 because of rounding.

Table 2. Trial Outcomes.*

Outcome	Endovascular Thrombectomy (N=327)	Alteplase with Endovascular Thrombectomy (N=329)	Measure of Effect	Adjusted Value (95% CI)
Primary outcome: modified Rankin Scale score at 90 days				
No. of patients with data	326	328		
Median score (IQR)	3 (2–5)	3 (2–5)	Common odds ratio	1.07 (0.81 to 1.40)
Secondary outcomes				
Clinical outcomes				
Modified Rankin scale score at 90 days according to range — no. (%)				
0 or 1	80 (24.5)	74 (22.5)	Odds ratio	1.09 (0.74 to 1.59)
0 to 2	119 (36.4)	121 (36.8)	Odds ratio	0.97 (0.68 to 1.37)
0 to 3	182 (55.7)	169 (51.4)	Odds ratio	1.25 (0.89 to 1.76)
0 to 4	218 (66.7)	207 (62.9)	Odds ratio	1.25 (0.88 to 1.77)
0 to 5	268 (82.0)	266 (80.9)	Odds ratio	1.10 (0.73 to 1.67)
Median NIHSS score (IQR)†				
After 24 hr	12 (5 to 20)	12 (5 to 22)	Beta coefficient	−0.52 (−2.13 to 1.09)
At 5–7 days or discharge	8 (2 to 16)	8 (2 to 19)	Beta coefficient	−1.26 (−3.20 to 0.68)
Barthel Index of 95 or 100 at 90 days — no./total no. (%)‡	156/326 (47.9)	151/328 (46.0)	Odds ratio	1.09 (0.78 to 1.53)
Median EQ-5D-5L score at 90 days (IQR)§	0.84 (0.48 to 0.95)	0.85 (0.26 to 1.00)	Beta coefficient	0.00 (−0.06 to 0.07)
Imaging outcomes				
Successful reperfusion before thrombectomy, as assessed on initial DSA — no. (%)¶	8 (2.4)	23 (7.0)	Odds ratio	0.33 (0.14 to 0.74)
eTICI score of 2b, 2c, or 3, as assessed on final angiogram — no./total no. (%)‖	243/306 (79.4)	267/316 (84.5)	Odds ratio	0.70 (0.47 to 1.06)
Recanalization at 24–72 hr, as assessed on CTA — no./total no. (%)**	240/282 (85.1)	245/275 (89.1)	Odds ratio	0.71 (0.42 to 1.20)
Median lesion volume on CT (IQR) — ml††	36.3 (9.8 to 114.8)	36.7 (9.6 to 99.2)	Beta coefficient	3.78 (−9.43 to 16.99)

* Values were adjusted for age, the NIHSS score at baseline, the time from stroke onset to randomization, the modified Rankin Scale score before stroke onset, and cerebral collateral blood-flow status. Confidence intervals for secondary outcomes, including imaging outcomes, were not adjusted for multiple comparisons, and no clinical inferences can be made from differences between groups. CTA denotes computed tomographic angiography, and DSA digital subtraction angiography.

† The NIHSS score was determined for survivors only. The score after 24 hours was not available for 37 patients: 19 died before the assessment was finished, and 18 had missing scores. The score at 5 to 7 days or discharge was not available for 86 patients: 63 died before the assessment was finished, and 23 had missing scores. The worst scores were assigned for dead patients, according to the statistical analysis plan.

‡ The Barthel Index is an ordinal scale for measuring performance of self care activities of daily living. Scores ranges from 0 to 100, with 0 indicating severe disability and 95 or 100 indicating no disability that interferes with daily activities. The worst scores were assigned for dead patients, according to the statistical analysis plan.

§ The EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L) is a standardized instrument for the measurement of health status. Scores range from −0.39 to 1.00, with higher scores indicating better quality of life.

¶ Successful reperfusion before thrombectomy was defined as an eTICI score of 2b, 2c, or 3 on the first intracranial angiogram.

‖ An eTICI score of 2b, 2c, or 3 indicated successful reperfusion. A total of 17 angiographic images could not be assessed for eTICI because of poor image quality (Table S5).

** Recanalization was defined as complete recanalization of the primary intracranial occlusion according to the modified Arterial Occlusive Lesion score.[1] Data for follow-up CTA were not available for 99 patients because of seriously illness or death.

†† Data for the final infarct volume on CT without the use of contrast material (performed at 3 to 10 days) were missing for 168 patients (86 in the thrombectomy-alone group and 82 in the combination-therapy group). The median follow-up time was 6.1 days (IQR, 5.7 to 6.8) in the thrombectomy-alone group and 6.1 days (IQR, 5.7 to 6.7) in the combination-therapy group.

Table 3. Serious Adverse Events within 90 Days (Intention-to-Treat Population).*

Variable	Endovascular Thrombectomy (N=327)	Alteplase with Endovascular Thrombectomy (N=329)	Risk Ratio (95% CI)	P Value
	number (percent)			
Safety outcomes				
Death	58 (17.7)	62 (18.8)	0.94 (0.68–1.30)	0.71
Asymptomatic intracranial hemorrhage	109 (33.3)	119 (36.2)	0.92 (0.75–1.14)	0.45
Symptomatic intracranial hemorrhage†	14 (4.3)	20 (6.1)	0.70 (0.36–1.37)	0.30
Infarction in new territory at 5–7 days	11 (3.4)	9 (2.7)	1.23 (0.52–2.93)	0.64
Other adjudicated serious adverse events				
Large or malignant MCA infarction	42 (12.8)	43 (13.1)	0.98 (0.66–1.46)	0.93
Pneumonia, aspiration or other	49 (15.0)	45 (13.7)	1.10 (0.75–1.59)	0.63
Allergic reaction to contrast material	1 (0.3)	1 (0.3)	1.01 (0.06–16.02)	1.00
Other	15 (4.6)	24 (7.3)		
Procedural complications‡				
Any procedural complication	49 (15.0)	47 (14.3)	1.05 (0.72–1.52)	0.80
Vessel dissection	8 (2.4)	5 (1.5)		
Contrast extravasation	6 (1.8)	10 (3.0)		
Embolization into a new territory	35 (10.7)	31 (9.4)		
Femoral access complications	2 (0.6)	1 (0.3)		

* Serious adverse events were observed in 121 patients (37.0%) in the thrombectomy-alone group and in 121 (36.8%) in the combination-therapy group. MCA denotes middle cerebral artery.
† Symptomatic intracranial hemorrhage was evaluated by an adverse-event committee according to the Heidelberg criteria.[24]
‡ Patients may have had multiple complications. A total of 85 patients (44 in the thrombectomy-alone group and 41 in the combination-therapy group) had uneventful artery vasospasm during the procedure; the majority of these events occurred in the extracranial ICA and were related to the guiding catheter.

ence from usual practice also means that the results of the trial may not apply to the common circumstance of administering intravenous alteplase at one hospital and sending the patient to another hospital for endovascular thrombectomy. In those instances, the intravenous infusion is usually completed before thrombectomy.

Because previous studies have reported differences in causes of stroke between Asian and non-Asian populations, our results may not be generalizable. However, only 6.9% of the patients in our trial had intracranial atherosclerotic disease, a prevalent cause of stroke among Asians.

Our trial has limitations. First, it was designed in accordance with the 2015 AHA–ASA guidelines,[18] in which stent retrievers were recommended for thrombectomy and intravenous thrombolysis was restricted to standard doses of alteplase. Recently, newer thrombectomy devices such as aspiration catheters and thrombolytic drugs such as tenecteplase have been used to treat stroke. Second, the prespecified noninferiority margin was generous, the sample was small, and there were wide confidence intervals around the primary outcome results; the implications for the possibility of an advantage with combined therapy have been mentioned earlier. Given the short time that was allowed for alteplase to act before endovascular treatment was initiated, the interpretation of our results across different systems of stroke care should be cautious.

Third, the prehospital triage system is more complicated in China than in many Western countries, with patients often traveling by personal transport directly to the hospital, and stroke teams are usually mobilized only on hospital admission rather than before the patients' arrival. Furthermore, informed consent is required before the administration of alteplase in China, and counseling before treatment commonly involves many

family members and is time-consuming. Consequently, workflow times were relatively long in our trial. Although there was a minimal difference between the groups with regard to treatment times, issues regarding payment by patients for alteplase in some centers could have prolonged the interval to treatment, which might have disadvantaged the group receiving combined therapy.

Our trial showed that among patients with acute ischemic stroke with large-vessel occlusion in the anterior circulation who were eligible for treatment with both intravenous alteplase and endovascular thrombectomy, endovascular thrombectomy alone was noninferior to thrombectomy preceded by alteplase administered within 4.5 hours after symptom onset, within a relative margin in the confidence interval of 20% in the shift between categories of the modified Rankin scale at 90 days. Larger trials in other populations are needed to compare alteplase plus endovascular therapy with endovascular therapy alone.

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APPENDIX

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