

Effect of Endovascular Treatment Alone vs Intravenous Alteplase Plus Endovascular Treatment on Functional Independence in Patients With Acute Ischemic Stroke

The DEVT Randomized Clinical Trial

Wenjie Zi, MD; Zhongming Qiu, MD; Fengli Li, MD; Hongfei Sang, MD; Deping Wu, MD; Weidong Luo, MD; Shuai Liu, MD; Junjie Yuan, MD; Jiaying Song, MD; Zhonghua Shi, MD; Wenguo Huang, MD; Min Zhang, MS; Wenhua Liu, MD; Zhangbao Guo, MS; Tao Qiu, MD; Qiang Shi, MS; Peiyang Zhou, MD; Li Wang, MD; Xinmin Fu, MD; Shudong Liu, MD; Shiquan Yang, MD; Shuai Zhang, MD; Zhiming Zhou, MD; Xianjun Huang, MD; Yan Wang, MD; Jun Luo, MS; Yongjie Bai, MD; Min Zhang, MS; Youlin Wu, MS; Guoyong Zeng, MD; Yue Wan, MD; Changming Wen, MD; Hongbin Wen, MD; Wentong Ling, MS; Zhuo Chen, MS; Miao Peng, MS; Zhibing Ai, MD; Fuqiang Guo, MD; Huagang Li, MD; Jing Guo, MS; Haitao Guan, MD; Zhiyi Wang, MS; Yong Liu, MS; Jie Pu, MD; Zhen Wang, MD; Hansheng Liu, MD; Luming Chen, MD; Jiacheng Huang, MD; Guoqiang Yang, MD; Zili Gong, MD; Jie Shuai, MD; Raul G. Nogueira, MD; Qingwu Yang, MD, PhD; for the DEVT Trial Investigators

IMPORTANCE For patients with large vessel occlusion strokes, it is unknown whether endovascular treatment alone compared with intravenous thrombolysis plus endovascular treatment (standard treatment) can achieve similar functional outcomes.

OBJECTIVE To investigate whether endovascular thrombectomy alone is noninferior to intravenous alteplase followed by endovascular thrombectomy for achieving functional independence at 90 days among patients with large vessel occlusion stroke.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, noninferiority trial conducted at 33 stroke centers in China. Patients (n = 234) were 18 years or older with proximal anterior circulation intracranial occlusion strokes within 4.5 hours from symptoms onset and eligible for intravenous thrombolysis. Enrollment took place from May 20, 2018, to May 2, 2020. Patients were enrolled and followed up for 90 days (final follow-up was July 22, 2020).

INTERVENTIONS A total of 116 patients were randomized to the endovascular thrombectomy alone group and 118 patients to combined intravenous thrombolysis and endovascular thrombectomy group.

MAIN OUTCOMES AND MEASURES The primary end point was the proportion of patients achieving functional independence at 90 days (defined as score 0-2 on the modified Rankin Scale; range, 0 [no symptoms] to 6 [death]). The noninferiority margin was -10%. Safety outcomes included the incidence of symptomatic intracerebral hemorrhage within 48 hours and 90-day mortality.

RESULTS The trial was stopped early because of efficacy when 234 of a planned 970 patients had undergone randomization. All 234 patients who were randomized (mean age, 68 years; 102 women [43.6%]) completed the trial. At the 90-day follow-up, 63 patients (54.3%) in the endovascular thrombectomy alone group vs 55 (46.6%) in the combined treatment group achieved functional independence at the 90-day follow-up (difference, 7.7%, 1-sided 97.5% CI, -5.1% to ∞) P for noninferiority = .003). No significant between-group differences were detected in symptomatic intracerebral hemorrhage (6.1% vs 6.8%; difference, -0.8%; 95% CI, -7.1% to 5.6%) and 90-day mortality (17.2% vs 17.8%; difference, -0.5%; 95% CI, -10.3% to 9.2%).

CONCLUSIONS AND RELEVANCE Among patients with ischemic stroke due to proximal anterior circulation occlusion within 4.5 hours from onset, endovascular treatment alone, compared with intravenous alteplase plus endovascular treatment, met the prespecified statistical threshold for noninferiority for the outcome of 90-day functional independence. These findings should be interpreted in the context of the clinical acceptability of the selected noninferiority threshold.

TRIAL REGISTRATION Chinese Clinical Trial Registry: ChiCTR-IOR-17013568

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The DEVT Trial Investigators appear in [Supplement 1](#).

Corresponding Authors: Qingwu Yang, MD, PhD, Department of Neurology, Xinqiao Hospital and The Second Affiliated Hospital, Army Medical University (Third Military Medical University), No. 183 Xinqiao Main St, Shapingba District, Chongqing 400037, China (yangqwmls@163.com); Raul G. Nogueira, MD, Department of Neurology, Marcus Stroke & Neuroscience Center, Grady Memorial Hospital, Emory University School of Medicine, 80 Jesse Hill Jr Dr SE, Room 8D108A, Atlanta, GA 30303 (raul.g.nogueira@emory.edu).

Seven randomized clinical trials have consistently demonstrated that patients with a large vessel occlusion in the anterior circulation benefit from endovascular treatment following intravenous thrombolysis (IVT).¹⁻⁷ However, IVT prior to endovascular treatment has potential benefits and risks. Intravenous thrombolysis may sometimes contribute to reperfusion, averting the need for endovascular treatment.⁵ Intravenous thrombolysis may facilitate endovascular reperfusion and promote dissolution of downstream microemboli improving distal perfusion.^{8,9} Conversely, IVT may increase the risk of intracranial or systemic hemorrhage, lead to thrombus fragmentation and worsening distal perfusion, and delay the start of the endovascular treatment.^{10,11} Furthermore, IVT limits the use of antithrombotic therapy within 24-hour, and increases health care costs.¹²

The recently reported randomized clinical trial of Endovascular Thrombectomy With or without Intravenous Alteplase in Acute Stroke (DIRECT-MT) showed that endovascular thrombectomy alone was noninferior to thrombectomy after IVT.¹³ Similar effect directions were seen in the SKIP trial,¹⁴ although this study was underpowered and, as such, was unable to demonstrate significance for noninferiority. The aim of the Direct Endovascular Thrombectomy vs Combined IVT and Endovascular Thrombectomy for Patients With Acute Large Vessel Occlusion in the Anterior Circulation (DEVT) trial was to test the hypothesis that endovascular thrombectomy alone was noninferior to combined IVT and endovascular thrombectomy in patients with proximal anterior circulation occlusions treated within 4.5 hours of onset.

Methods

Trial Design and Oversight

This trial was a multicenter, randomized, open-label, clinical trial with blinded central evaluation of outcomes in patients with stroke. The trial protocol was approved by medical ethics committee of the Second Affiliated Hospital of the Army Medical University and all participating centers. Written informed consent was obtained from all enrolled patients or their legal representatives before randomization. The trial protocol is available in [Supplement 2](#), the statistical analysis plan, in [Supplement 3](#).

The trial was monitored by an independent data and safety monitoring board. An independent clinical events committee validated adverse events, procedural-related complications, and serious adverse events. All images were assessed in a blinded manner by a core laboratory. The methods of this trial have been published previously.¹⁵ [eFigure 1 in Supplement 4](#) shows planned trial assessments and interventions.

Participating Centers and Patients

The study was conducted at 33 stroke centers in China. To qualify for participation, each center had to perform more than 50 mechanical thrombectomies annually and each neurointerventionist, at least 10 thrombectomies per year. To ensure the quality of the trial, training of study protocol and endovascular treatment technique was held every 6 months in Chongqing ([eMethods 4 in Supplement 4](#)).

Key Points

Question Among patients with ischemic stroke secondary to large vessel occlusion and eligible for thrombolysis, is endovascular treatment alone noninferior to intravenous alteplase plus endovascular treatment with regard to functional independence?

Findings In this randomized clinical trial that included 234 patients with acute ischemic stroke, the proportion who achieved functional independence at 90 days was 54.3% in the endovascular treatment alone group vs 46.6% in the intravenous alteplase plus endovascular treatment group, a difference that met the prespecified noninferiority margin of 10%.

Meaning Among patients with acute ischemic stroke due to large vessel occlusion and eligible for thrombolysis, endovascular treatment alone, compared with intravenous alteplase plus endovascular treatment, met the prespecified statistical threshold for noninferiority for the outcome of 90-day functional independence, although the clinical acceptability of the threshold for noninferiority should be considered when interpreting the results.

Study candidates were 18 years or older with acute ischemic stroke, eligible for IV alteplase treatment within 4.5 hours of onset, and had occlusion of the intracranial internal carotid artery or the first segment of the middle cerebral artery confirmed by computed tomographic (CT) angiography or magnetic resonance (MR) angiography. Time of stroke onset was defined as when the patient was last known to be well. Randomization was performed no later than 4 hours 15 minutes from onset ([Figure 1](#)). The main exclusion criteria were imaging evidence of intracranial hemorrhage and pre-morbidity with a modified Rankin Scale score of 2 or more (mRS; range, 0 [no symptoms] to 6 [death]). Additional detailed study criteria are provided in [eMethods 1 in Supplement 4](#). Central blinded readers assigned a collateral score using the 5-point American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral flow grading scale (range, 0 [no collaterals visible] to 4 [complete or rapid collaterals to entire ischemic territory]).

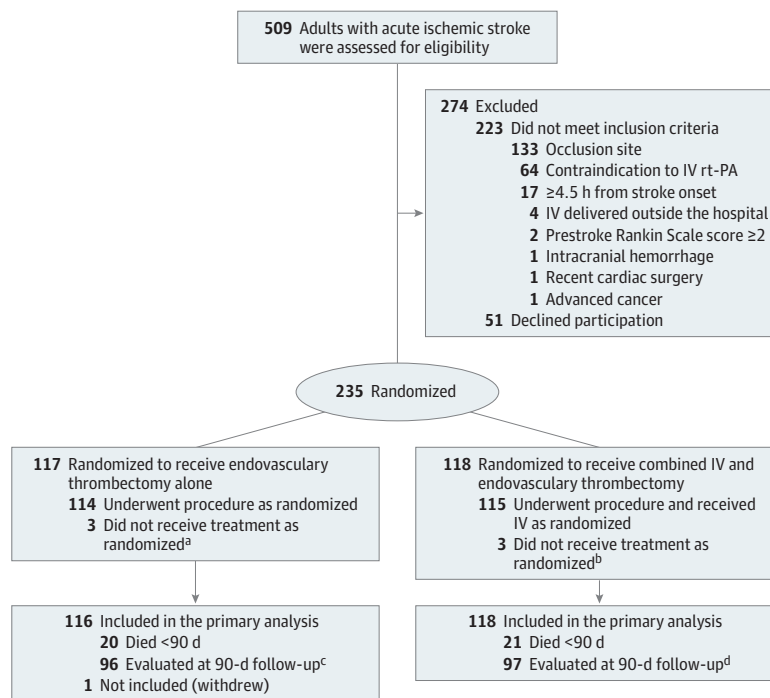
Randomization and Masking

Patients were randomized in a 1:1 ratio to either the endovascular thrombectomy alone group or combined IV thrombolysis and endovascular thrombectomy group. The randomization procedure was web-based, and competitive recruitment was applied in this trial. Randomization allocations were created by an independent statistician with the use of SAS version 9.3 (SAS Institute Inc) to keep the study group blind. Four-block randomization was used. Personnel conducting clinical examinations were qualified assessors who had not participated in the study procedures.

Intervention

Patients in both groups received rapid endovascular treatment. In the endovascular thrombectomy alone group, patients underwent endovascular treatment only, which

Figure 1. Eligibility, Randomization, and Follow-up of Patients Through the DEVT Randomized Clinical Trial of Intravenous Alteplase in Patients With Acute Ischemic Stroke



^a One patient had expanded Thrombolysis in Cerebral Infarction (eTICI) 3 on the first intracranial angiography; the other, eTICI 2c on first intracranial angiography. One patient withdrew immediately after randomization.

^b One patient had eTICI 2c on first intracranial angiography; 2 had eTICI 2b on first intracranial angiography.

^c Of the survivors, 91 had video recording, 4 had voice recording, 1 outcome determined by local investigators blinded to the treatment assignments because video or voice recording was unavailable.

^d Of the survivors, 95 had video recording, 2 had voice recording. 0 outcomes determined by local investigators blinded to the treatment assignments.

DEVT indicates Direct Endovascular Thrombectomy vs Combined IV Thrombolysis and Endovascular Thrombectomy for Patients With Acute Large Vessel Occlusion in the Anterior Circulation Trial; IV indicates intravenous; rt-PA, recombinant tissue type plasminogen activator.

included thrombectomy with stent retrievers, thromboaspiration, intraarterial thrombolysis, balloon angioplasty, stenting, or a combination of these approaches at the discretion of the treatment team.

Patients in the combined treatment group underwent the endovascular procedure after receiving a standard dose of IV alteplase (0.9 mg/kg of body weight; 10% administered as a bolus followed by 1-hour infusion of the remaining dose). Endovascular treatment was initiated as soon as possible without waiting for clinical response from IV alteplase. The full alteplase dose was infused even if successful reperfusion had already been established.

Outcome and Safety Measures

The primary outcome was the proportion of patients achieving functional independence (mRS score, 0-2) at 90 days (+/- 14 days), with central evaluation by 2 blinded independent mRS-certified neurologists based on video or voice recordings taken at the outpatient clinic, during a telephone or video call, or by the patient's family. If video or voice recordings were unavailable, the outcomes were determined in person by local investigators blinded to the treatment assign-

ments. Disagreements were resolved through consensus (eMethods 3 in Supplement 4).

Secondary outcomes included the distribution of 90-day mRS scores and the rates of excellent functional outcome (mRS score, 0-1), successful reperfusion on postprocedural angiography (grade 2b-3 on the expanded Thrombolysis in Cerebral Infarction [eTICI] scale, indicating reperfusion of ≥50% of the affected territory),¹⁶ vessel reperfusion on CT or MR angiography within 48 hours after treatment (successful recanalization was defined by a core laboratory-adjudicated modified Arterial Occlusive Lesion score of 2 or 3 on CT or MR angiography, indicating partial or complete recanalization of the occluded artery), the change of the National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher values indicating more severe deficit) from baseline to 24 hours and 5 to 7 days (or discharge if earlier), and score of European Quality of Life 5-Dimension 5-level scale (EQ-5D-5L; range, -0.39 to 1, higher scores indicate a better quality of life) at 90 days. The NIHSS assessment was based on central evaluation through video recording or, if recording was unavailable, by blinded local investigators. A post hoc analysis evaluated the rates of successful reperfusion before

endovascular treatment (defined as an eTICI score of 2b, 2c, or 3 on the initial intracranial angiogram).

Adverse events, including incidence of symptomatic intracranial hemorrhage within 48 hours, 90-day mortality, procedure-associated complications, and serious adverse events, were adjudicated by an independent clinical events committee unaware of treatment assignment. Assessment of intracranial hemorrhage was based on the Heidelberg classification.¹⁷ A post hoc analysis investigated the rates of asymptomatic and symptomatic intracranial hemorrhage using the European Cooperative Acute Stroke Study III (ECASS III), ECASS II, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), and the National Institute of Neurological Disorders and Stroke (NINDS) definitions.

Statistical Analysis

The primary hypothesis was that the rate of 90-day functional independence with endovascular treatment alone would be noninferior to IV alteplase plus endovascular treatment, the primary aim of the statistical analysis. Sample size calculation was made assuming that 43% of patients in both groups would achieve functional independence at the 90-day follow-up according to previous studies.¹⁸⁻²⁰ Among the recent high-quality randomized clinical trials, the endovascular group in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)⁶ trial had the lowest proportion (about 33%) of 90-day functional independence. We assumed that the proportion of patients achieving 90-day functional independence of the endovascular thrombectomy alone group could not be lower than 33%. Therefore, the noninferiority margin was set at -10.0% as the clinically relevant limit for the outside bound of the CI.

A sample size of 918 patients (459 patients per group) would provide 80% statistical power to show noninferiority of endovascular thrombectomy alone group compared with combined treatment group including a 5-interim group-sequential analysis plan, using a 1-sided significance level of .025 and a noninferiority margin of 10% of the functional independence proportion in the combined treatment group. To adjust for a 5% attrition rate, the total sample size increased to 970. The evaluable sample size was 194 at each interim analysis (97 patients in each group). The termination rule for efficacy was defined by using the Pocock analog boundaries on the binary outcome of functional independence.²¹

The primary outcome was analyzed using a noninferiority test for the difference of 2 proportions. The adjusted odds ratio was estimated using a logistic regression model by taking the following variables into account: age, baseline NIHSS score, baseline Alberta Stroke Program Early Computed Tomography Score (ASPECTS), onset to randomization time, and occlusion site. Secondary outcomes were analyzed using a logistic, ordinal logistic, or linear regression model as appropriate. The Kaplan-Meier method was used to assess the mortality. The log-rank test was applied to compare the 2 treatment groups. Moreover, the death data of each treat-

ment group were reported as 90-day binary deaths. The post hoc hierarchical modeling and sensitivity analyses were performed to assess site effects.

The missing values of baseline variables were imputed with multiple imputation. Subgroup analyses were conducted for the primary effect variable, and the Wald χ^2 test was used to test the interaction. All enrolled patients were analyzed according to their randomization group. Patients who actually received the assigned treatment and did not have major protocol violations were included in the per-protocol analysis. The rates of successful reperfusion before endovascular treatment was analyzed post hoc. All statistical tests were 2-sided with a significance level at .05 unless otherwise noted. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. Statistical analyses were performed using SAS version 9.4. Figures were drawn using Excel software 2019 (Microsoft).

Trial Termination

The first interim analysis was performed as planned after 194 patients (20% of the maximum sample size) had completed their 90-day follow-up on May 12, 2020. The proportion of patients achieving functional independence for the endovascular thrombectomy alone group (54.64%) exceeded that of the combined treatment group (47.42%) by 7.2% (1-sided 97.5% CI, -6.8% to ∞). The noninferiority test demonstrated that endovascular thrombectomy alone was noninferior to combined treatment ($z = 2.4042$, P for noninferiority = .008). Because this crossed the prespecified efficacy boundary ($z = 2.35826$, P for noninferiority = .009) that was prespecified for early termination, the steering committee accepted the recommendation from the data and safety monitoring board of concluding the trial on May 14, 2020 (eMethods 2 and eFigure 2 in Supplement 4).

Results

Patients and Baseline Characteristics

From May 20, 2018, to May 2, 2020, a total of 509 patients across 33 stroke centers in China were screened. Among them, 235 qualified and were randomly enrolled in the trial. One patient enrolled into the endovascular thrombectomy alone group could not be included in the analysis because the legal representative withdrew consent immediately after randomization. The median age of the 234 patients was 70 years (interquartile range [IQR], 60-78 years); 132 patients (56.4%) were men. Of 234 patients, 116 were randomized to the endovascular thrombectomy alone group and 118 to combined treatment group. No crossovers occurred, and no one was lost to the 90-day follow-up. Baseline characteristics were similar in both groups (Table 1; eTable 1 in Supplement 4). The distribution of participating centers is illustrated on the map of China (eFigure 3), another map shows the number of patients recruited at each center (eFigure 4), and the third map shows the enrollment and follow-up of patients (eFigure 5 in Supplement 4).

Table 1. Baseline Characteristics and Workflow Measures

	No. (%) of patients	
	Endovascular thrombectomy alone (n = 116)	Combined IV thrombolysis and endovascular thrombectomy (n = 118)
Demographic characteristics		
Age, median (IQR), y	70 (60-77)	70 (60-78)
Sex		
Men	66 (56.9)	66 (55.9)
Women	50 (43.1)	52 (44.1)
Medical history ^a		
Hypertension	69 (59.5)	74 (62.7)
Atrial fibrillation	62 (53.5)	62 (52.5)
Coronary heart disease ^b	30 (25.9)	19 (16.1)
Smoking ^c	28 (24.1)	29 (24.6)
Diabetes	25 (21.6)	20 (17.0)
Hyperlipidemia	18 (15.5)	22 (18.6)
Ischemic stroke	14 (12.1)	19 (16.1)
Prestroke score on the modified Rankin Scale of 1 ^d	6 (5.2)	11 (9.3)
Stroke etiology		
Cardioembolism	65 (56.0)	69 (58.5)
Large artery atherosclerosis	32 (27.6)	28 (23.7)
Intracranial atherosclerosis	28 (24.1)	23 (19.5)
Unknown	15 (12.9)	20 (16.9)
Other ^e	4 (3.4)	1 (0.8)
Imaging characteristics^f		
Baseline ASPECTS, No. ^g	115	117
Median (IQR)	8 (7-9)	8 (7-9)
Occlusion site on CT or MR angiography		
Intracranial internal carotid artery	18 (15.5)	17 (14.4)
M1 middle cerebral artery segment	95 (81.9)	99 (83.9)
M2 middle cerebral artery segment	3 (2.6)	2 (1.7)
Clinical examination at arrival, median (IQR)		
NIHSS score ^h	16 (12-20)	16 (13-20)
Systolic blood pressure, mm Hg ⁱ	146 (129-165)	145 (128-168)
Glucose level, mmol/L	6.7 (5.7-8.1)	6.9 (5.9-8.9)
No. of patients	114	115
Workflow times, median (IQR), min		
Onset to randomization ^l	170 (129-204)	168 (144-216)
Arrival to intravenous alteplase	NA	61 (49-81)
Arrival to arterial puncture	101 (80-135)	105 (80-132)
Onset to puncture ^j	200 (155-247)	210 (179-255)

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; IQR, interquartile range; IV, intravenous; MR, magnetic resonance; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale.

SI conversion factor: To convert glucose from mmol/L to mg/dL, divide by 0.0555.

^a Patient self-report or family report.

^b Included self-reported coronary artery bypass grafting surgery, angina pectoris (confirmed by angiogram), angioplasty, or coronary artery stents, besides myocardial infarction.

^c Current or within the prior 5 years.

^d See the Methods section for functional disability ranges. A score of 2 or less indicates functional independence. The score before onset was evaluated with patients or families through the specified Rankin Structured interview. Only patients with scores of 0 or 1 were enrolled.

^e The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification assessed stroke etiology; other causes included small vessel occlusion, nonatherosclerotic vasculopathies, hypercoagulable states, and hematologic disorders.

^f Imaging characteristics were assessed by the imaging core laboratory.

^g Imaging measures the extent of ischemic stroke (range, 0-10, higher scores indicate smaller infarct core). Listed are values for the core laboratory assessment.

^h National Institutes of Health Stroke Scale (NIHSS) score (range, 0-42, lower scores indicate less severe neurological deficits).

ⁱ Assessed at enrollment; antihypertensives were not permitted prior to determination of inclusion.

^j Onset from patient or witness. Unknown times were the last known time well as reported by a proxy.

Primary Outcome

Among the patients who survived and were followed up to 90 days, video materials were acquired from 186 patients and voice recordings from 6 patients. One patient's assessment was determined by local investigators blinded to the treatment assignments because video or voice recording technology was unavailable. Sixty-three patients (54.3%) in the endovascular thrombectomy alone group achieved functional independence vs 55 patients (46.6%) in the combined treatment group (difference, 7.7%; 1-sided 97.5% CI, -5.1% to ∞; Table 2). The lower boundary of the CI of -5.1% and was greater than the prespecified noninferiority margin

of -10%. In addition, the noninferiority test demonstrated that the endovascular thrombectomy alone was noninferior to the combined IV thrombolysis and endovascular thrombectomy group ($z = 2.7157$, P for noninferiority = .003) since it crossed the efficacy boundary ($z = 2.35826$, P for noninferiority = .009) that was prespecified for early termination. The per-protocol analysis indicated that results were consistent with the primary analysis (eTable 3 and eTable 4 in Supplement 4). Prespecified subgroup analyses are shown in eFigures 6 and 7 (Supplement 4), and the post hoc hierarchical modeling and sensitivity analyses indicate that the site effects were not significant (eTable 5 in Supplement 4).

Table 2. Modified Rankin Scale Score at 90 Days and Secondary Outcomes

	No. (%)				
	Endovascular thrombectomy alone (n = 116)	Combined IV thrombolysis and endovascular thrombectomy (n = 118)	Unadjusted difference (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI) ^a
Primary efficacy outcome ^b					
Functional independence ^c	63 (54.3)	55 (46.6)	7.7 (-5.1 to ∞) ^d	1.36 (0.82 to 2.28)	1.48 (0.81 to 2.74)
Secondary efficacy outcomes					
Excellent outcome ^c	44 (37.9)	37 (31.4)	6.6 (-5.6 to 18.7)	1.34 (0.78 to 2.30)	1.38 (0.75 to 2.56)
Disability level, median (IQR), mRS score ^c	2 (1 to 4)	3 (1 to 4)	0 (-1 to 0)	1.17 (0.75 to 1.84) ^e	1.13 (0.71 to 1.79) ^e
Successful reperfusion (eTICI 2b-3) at final angiogram ^f	100 (88.5)	102 (87.2)	1.3 (-7.1 to 9.8)	1.13 (0.51 to 2.53)	1.14 (0.50 to 2.61)
No.	113	117			
Reperfusion on follow-up CT or MR angiography ≤48 h ^g	96 (97.0)	94 (93.1)	3.9 (-2.1 to 9.9)	2.38 (0.64 to 11.31)	2.37 (0.63 to 11.34)
No.	99	101			
NIHSS score, median (IQR), change from baseline				β Coefficient (95% CI) ^h	
24 h ⁱ	-4 (-8 to 0)	-3 (-6 to -1)	-1 (-2 to 1)	-0.14 (-1.97 to 1.69)	-0.26 (-2.06 to 1.54)
5 to ≈7 d or early discharge ⁱ	-7 (-11 to -1)	-6 (-10 to -2)	0 (-2 to 2)	1.02 (-1.76 to 3.80)	0.77 (-1.96 to 3.50)
Health-related quality of life, EQ-5D-5L score, median (IQR) ^j	0.89 (0.22 to 1.00)	0.74 (0.26 to 0.96)	0.00 (0.00 to 0.05)	0.04 (-0.06 to 0.14)	0.04 (-0.04 to 0.13)

Abbreviations: CT, computed tomography; EQ-5D-5L, European Quality of Life 5-Dimensions 5-Levels questionnaire; eTICI, Expanded Thrombolysis In Cerebral Infarction; IQR, interquartile range; IV, intravenous; MR magnetic resonance; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

^a Values were adjusted for age, baseline NIHSS and Alberta Stroke Program Early Computed Tomography Score, occlusion site, and time from onset to randomization.

^b Noninferiority test for the difference of 2 proportions.

^c See the Methods section for mRS score ranges and evaluation criteria.

^d Indicates 1-sided 97.5% CI.

^e The common odds ratio was estimated from an ordinal logistic regression model and indicates the odds of improvement of 1 point on the mRS, with a common odds ratio greater than 1 favoring the endovascular thrombectomy treatment alone group.

^f The eTICI grade was determined at the final angiogram (range, 0 [no reperfusion] to 3 [completed reperfusion]). A score of 2b to 3 indicates successful reperfusion. Data were missing from 3 patients in the endovascular thrombectomy alone group and 1 in the combined treatment group. A complete list of eTICI grades is provided in eTable 2 in Supplement 3.

^g Data were not available for 23 patients (12 in the endovascular thrombectomy alone group; 11 in the combined treatment group). Reperfusion failed in 11 patients (5 in the endovascular thrombectomy alone group and 6 in the combined treatment group). Vessel patency was adjudicated by 2 blinded independent neuroradiologists. Disagreements were resolved by consensus.

^h The β coefficient was estimated from a multivariable linear regression model.

ⁱ Lower scores (range, 0-42), indicate less severe neurological deficits.

^j Higher scores (range, -0.39 to 1) indicate better quality of life; 0 is the value of a health state equivalent to death; negative values, worse than death; 1, full health.

Secondary Outcomes

The median of 90-day mRS scores for endovascular thrombectomy alone was 2 (IQR, 1-4) and for the combined treatment, 3 (IQR, 1-4). The unadjusted difference was 0 (95% CI, -1 to 0). The adjusted common odds ratio was 1.13 (95% CI, 0.71-1.79). There were no significant differences in other secondary efficacy outcomes (Table 2). In a post hoc analysis, successful reperfusion before endovascular treatment assessed on initial angiography was observed for 2 patients in the endovascular thrombectomy alone and 3 in the combined IV thrombolysis and endovascular thrombectomy group (1.7% vs 2.6%). Further details are provided in the Table 2 and Figure 2.

Safety Outcomes

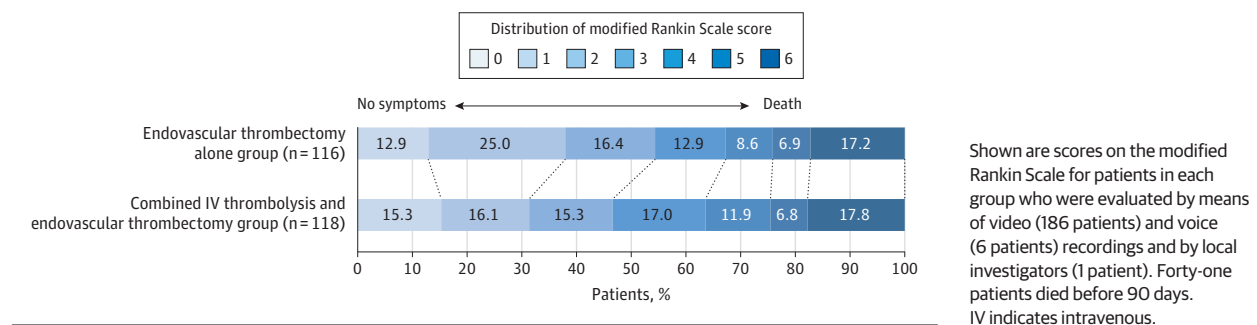
The proportion of patients who died within 90 days was 17.2% among those in the endovascular thrombectomy alone group vs 17.8% among those in the combined treatment group (difference, -0.5%; 95% CI, -10.3% to 9.2%). According to the Heidelberg bleeding classification, the symptomatic intracere-

bral hemorrhage in the 2 groups was 6.1% vs 6.8% (difference, -0.8%; 95% CI, -7.1% to 5.6%), respectively. Furthermore, in post hoc analyses, based on other definitions, the rate of symptomatic intracranial hemorrhage did not differ significantly between the 2 groups (Table 3). In a post hoc analysis, asymptomatic intracerebral hemorrhage occurred in 15.7% vs 25.6% (difference, -10.0%; 95% CI, -20.3% to 0.3%), respectively. Clot migration occurred in 20 patients (17.7%) of 113 in the endovascular thrombectomy alone group vs 28 of 117 (23.9%) in combined treatment group. There were no significant differences in proportions of procedures associated complications or serious adverse events (Table 3). Kaplan-Meier estimates of the probability of death are provided in eFigure 5 in Supplement 4.

Discussion

In this randomized clinical trial involving patients with ischemic stroke who presented within 4.5 hours from onset, had

Figure 2. Distribution of the Modified Rankin Scale Score at 90 Days



proximal anterior circulation occlusion, and were eligible for intravenous alteplase, endovascular thrombectomy alone, compared with combined IV alteplase and endovascular thrombectomy, met the prespecified statistical threshold for noninferiority for achieving 90-day functional independence. Different from the prior trials, this present trial excluded participants with middle cerebral artery M2 segment occlusion and used a full dose of alteplase.

The rate of 90-day functional independence with combined IV thrombolysis and endovascular thrombectomy in this trial was 46.6%, which is similar to the 46.4% observed in the Highly Effective Reperfusion Using Multiple Endovascular Devices (HERMES) meta-analysis.²³ However, the overall frequency of 90-day functional independence in this study was higher (50.4%) than that observed in the Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals (DIRECT-MT) trial (36.6%).¹³ The potential explanations for these differences include that the intracranial internal carotid artery occlusions occurred more frequently in the DIRECT-MT trial (35%) than in either this trial (15%) or the HERMES trial (21%), whereas the patients with favorable collateral status (defined as grade 2-3 on the ASITN/SIR scale) had fewer in the DIRECT-MT trial (24%) than patients in either this trial (68.4%) or the HERMES trial (85%).^{13,24}

More patients participating in both groups in this study achieved 90-day functional independence than patients in the DIRECT-MT trial. This provided an important supplement of noninferiority despite the early termination and consequent smaller sample size in the current study. That middle cerebral artery M2 occlusions were excluded from this trial, which are known to have a better response to IVT,²⁵ may have contributed to the differences across the 2 trials. Indeed, higher rates of successful reperfusion prior to thrombectomy were seen with combined IVT and endovascular thrombectomy in the DIRECT-MT trial but not in this trial. Some other factors that may have theoretically favored endovascular thrombectomy alone in this trial include the lower proportions of both clot migration (17.7% vs 23.9%) and asymptomatic intracranial hemorrhage (15.7% vs 25.6%) over combined IV thrombolysis and endovascular thrombectomy because both these factors appear to be associated with worse functional outcomes after endovascular stroke treatment.^{10,26}

A cohort study that used data from 2017 to 2019 and included 1526 patients showed that patients with asymptomatic intracranial hemorrhage have a worse functional outcome at 3 months than do those without it after endovascular treatment for acute ischemic stroke.²⁷ This observation may be attributed to the cytotoxic effect of the contrast agent and the mass effect caused by the destruction of the blood-brain barrier, compressing the adjacent healthy parenchyma with subsequent impairment of the functional recovery.²⁷

In comparing the results of this trial with those of the SKIP and DIRECT-MT trials, the rate of intracranial hemorrhage was similarly higher among patients in the combined treatment group this trial and in the SKIP trial (34% vs 50%, $P = .02$), even though patients in the SKIP trial received a lower dose of alteplase (0.6 mg/kg) than did the patients in this study. Conversely, patients in the DIRECT-MT trial had similar rates of asymptomatic intracranial hemorrhage between treatment groups (33.3% vs 36.2%). This could be partially because in the DIRECT-MT trial's combined IV thrombolysis and endovascular thrombectomy group, 30 patients (9.1%) did not receive either the full dose ($n = 20$) or any dose ($n = 10$) of alteplase, and 37 patients (11.2%) did not undergo thrombectomy. Moreover, eTable 6 lists other important factors—including trial design, inclusion criteria, primary end point—used in the DIRECT-MT and SKIP trials alongside those used in this trial (Supplement 4).

Limitations

This study has several limitations. First, the noninferiority margin used in this trial was not selected using the minimal clinically important difference or fixed margin methods. The noninferior margin of 10% is broad, reaching no consensus in the clinical community, which may lead to concerns about the robustness of study results. Second, the early termination of the trial does create potential for overestimation of the effect size. However, it followed a highly conservative prespecified statistical stopping rule.

Third, the median time from hospital arrival to the start of IV alteplase of 61 minutes (IQR, 49-81 minutes) in this trial was similar to the 59 minutes (IQR, 45-78 minutes) in the DIRECT-MT trial but was longer than what has been reported in the other recent thrombectomy trials.²⁻⁷ The main reason for these differences is that alteplase could not be administered immediately after standard clinical and neuroimaging

Table 3. Reported Severe Adverse Events and Procedure Associated Complications

	No./total (%)	
	Endovascular thrombectomy alone group (n = 116)	Combined IV thrombolysis and endovascular thrombectomy group (n = 118)
Patients with at least 1 serious adverse event	30 (25.9)	26 (22.0)
Any intracranial hemorrhage ^a	25/115 (21.7)	38/117 (32.5)
Symptomatic intracerebral hemorrhage definitions		
NINDS ^b	10/115 (8.7)	12/115 (10.3)
ECASS II ^c	9/115 (7.8)	10/117 (8.5)
HBC ^d	7/115 (6.1)	8/117 (6.8)
ECASS III ^e	5/115 (4.3)	7/117 (6.0)
SITS-MOST ^f	4/115 (3.5)	5/117 (4.3)
Mortality at 90 d	20 (17.2)	21 (17.8)
Acute respiratory failure ^g	14 (12.1)	12 (10.2)
Large or malignant middle cerebral artery stroke ^h	13 (11.2)	9 (7.6)
Acute heart failure ⁱ	12 (10.3)	9 (7.6)
Hemicraniectomy ^j	3 (2.6)	5 (4.2)
Patients with at least 1 procedure-associated complication ^k	34/113 (30.1)	48/117 (41.0)
Clot migration ^l	20/113 (17.7)	28/117 (23.9)
Distal occlusion present at procedure end ^m	19/113 (16.8)	21/117 (18.0)
Contrast extravasation ⁿ	16/115 (13.9)	17/117 (14.5)
Arterial perforation	2 (1.7)	6 (5.1)
Puncture access complications	1 (0.9)	6 (5.1)
Arterial dissection	0/113	1/117 (0.8)

Abbreviations: ECASS, European Cooperative Acute Stroke Study; HBC, Heidelberg bleeding classification; NINDS, National Institute of Neurological Disorders and Stroke; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

^a A complete list of intracranial hemorrhage classifications is provided in eTable 7 and definitions of symptomatic intracerebral hemorrhage in eTable 8 in Supplement 4. Data were not available for 1 patient in the endovascular thrombectomy alone group and 1 in the combined treatment group.

^b Symptomatic if hemorrhage had not been seen on a previous computed tomographic (CT) scan but either subsequent suspicion of hemorrhage or decline in neurological status existed.

^c The ECASS II was the same as ECASS III, except that establishment of a causal relationship between the hemorrhage and clinical deterioration or death was not a requirement.

^d Symptomatic intracerebral hemorrhage detected by brain imaging as a relevant change in neurological status; absence of another explanation for deterioration; an event leading to intubation, hemicraniectomy, or external ventricular draining placement; or other major medical or surgical intervention.

^e Any hemorrhage with neurological deterioration identified as the predominant cause.

^f Local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, plus neurological deterioration.

^g Need for mechanical ventilation or oxygen through a reservoir mask or a Pulmonary Severity Index greater than 130.

^h Any large infarction with mass effect observed on imaging that required medical or surgical treatment of mass effect.

ⁱ Brain natriuretic peptide (BNP) concentration, changes in N-terminal pro-BNP (NT-pro-BNP) or Killip class II or higher.

^j Surgical procedure to decompress the swollen hemisphere caused by large or malignant middle cerebral artery stroke.

^k All procedure-associated complications were reported by the clinical events committee.

^l Clot observed to have moved before and/or during the intervention at the occlusion site. Data were not available for 3 patients in the endovascular thrombectomy alone group and 1 in the combined treatment group.

^m Occurred after reperfusion of the primary occlusion site, any vessel occlusions distal from the primary occlusion site were considered emboli due to periprocedural thrombus fragmentation.

ⁿ Contrast extravasation is a hyperdense lesion with a maximum Hounsfield unit greater than 90 that persists on a follow-up CT scan.²² Data were not available for 1 patient in the endovascular thrombectomy alone group and 1 in the combined treatment group.

screening as they were in the previous trials because additional time was required for study screening, obtaining patient consent, and randomization in this and the DIRECT-MT trials. This explanation is supported by the findings of a recent multinational neuroprotection randomized trial. Despite having one of most efficient workflows for IVT and thrombectomy reported to date, the median time from hospital arrival to the initiation of the experimental drug in the Safety and Efficacy of Nerinetide in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE NA-1) trial was 64 minutes (IQR, 48-86 minutes).²⁸ This highlights that achieving hos-

pital arrival to initiate IV alteplase times as short as those in the previous trials with the absence of waiver of informed consent is unlikely.

In China, informed consent is required even before the standard administration of IVT because patients or their families often have to pay in advance before receiving alteplase. Relatedly, the median door-to-needle time was 62 minutes (IQR, 40-94 minutes) among 24 542 patients treated with IV alteplase in a recent analysis of the Chinese Stroke Center Alliance Program,²⁹ a finding that is fully consistent with the times seen in this and the DIRECT-MT trials.

Nevertheless, given the relatively long times from hospital arrival to alteplase initiation in this trial, it remains possible that IV alteplase might still be beneficial in the presence of faster delivery times. Moreover, as bridging with tenecteplase vs alteplase was associated with higher rates of prethrombectomy reperfusion and better 90-day functional outcomes in the Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke (EXTEND-IA-TNK) trial,³⁰ it is possible that tenecteplase bridging might yield better results than thrombectomy alone.

Fourth, because this, the DIRECT-MT, and the SKIP trials only included Asian patients, the generalizability of their findings is somewhat limited due to the significantly higher inci-

dence of intracranial atherosclerotic disease in Asian than in Western populations.

Conclusions

Among patients with ischemic stroke due to proximal anterior circulation occlusion within 4.5 hours from onset, endovascular treatment alone, compared with IV alteplase plus endovascular treatment, met the prespecified statistical threshold for noninferiority for the outcome of 90-day functional independence. These findings should be interpreted in the context of the clinical acceptability of the selected noninferiority threshold.

ARTICLE INFORMATION

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Author Affiliations: Department of Neurology, Xinqiao Hospital and The Second Affiliated Hospital, Army Medical University (Third Military Medical University), Shapingba District, Chongqing, China (Zi, Z. Qiu, F. Li, Sang, D. Wu, W. Luo, Shuai Liu, Yuan, Song, H. Liu, L. Chen, J. Huang, G. Yang, Gong, Shuai, Q. Yang); Department of Neurology, The 903rd Hospital of The Chinese People's Liberation Army, Xihu District, Hangzhou, China (Z. Qiu); Department of Neurology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China (Sang); Huaian Medical District of Jingling Hospital, Medical School of Nanjing University, Huaian, China (D. Wu); Department of Neurosurgery, The 904th Hospital of The Chinese People's Liberation Army, Wuxi, China (Z. Shi); Department of Neurology, Maoming Traditional Chinese Medicine Hospital, Maonan District, Maoming, China (W. Huang, Min Zhang); Department of Neurology, Wuhan No. 1 Hospital, Qiaokou District, Wuhan, China (W. Liu, Z. Guo); Department of Neurology, The First People's Hospital of Zigong, Da'an District, Zigong, China (T. Qiu, Q. Shi); Department of Neurology, The First People's Hospital of Xiangyang, Fancheng District, Xiangyang, China (P. Zhou); Department of Neurology, The Third People's Hospital of Zigong, Gongjing District, Zigong, China (L. Wang); Department of Neurology, Xuzhou Central Hospital, Quanshan District, Xuzhou, China (Fu); Department of Neurology, Yongchuan Hospital of Chongqing Medical University, Chongqing Key Laboratory of Cerebrovascular Disease Research, Yongchuan District, Chongqing, China (Shudong Liu); Department of Neurology, The 902nd Hospital of The Chinese People's Liberation Army, Yuhui District, Bengbu, China (S. Yang); Department of Neurology, The Affiliated Hospital of Yangzhou University, Guangling District, Yangzhou, China (S. Zhang); Department of Neurology, Yijishan Hospital of Wannan Medical College, Wuhu, China (Z. Zhou, X. Huang); Department of Neurology, The Fifth People's Hospital of Chengdu, Wenjiang District, Chengdu, China (Y. Wang); Department of Neurology, Sichuan Mianyang 404 Hospital, Fucheng District, Mianyang, China (J. Luo); Department of Neurology, The First Affiliated Hospital of Henan Science and Technology University, Jianxi District, Luoyang, China (Bai); Department of Neurology, Jiangmen Central Hospital, Pengjiang District, Jiangmen, China (Min Zhang); Department of Neurology, Chongzhou

People's Hospital, Chongzhou, China (Y. Wu); Department of Neurology, Ganzhou People's Hospital, Zhanggong District, Ganzhou, China (Zeng); Department of Neurology, Yangluo District of Hubei Zhongshan Hospital, Qiaokou District, Wuhan, China (Wan); Department of Neurology, Nanyang Central Hospital, Wolong District, Nanyang, China (C. Wen); Department of Neurology, Xiangyang Central Hospital, Xiangcheng District, Xiangyang, China (H. Wen); Department of Neurology, Zhongshan People's Hospital, Zhongshan, China (Ling); Department of Neurology, Mianzhu People's Hospital, Mianzhu, China (Z. Chen); Department of Neurology, Deyang People's Hospital, Jingyang District, Deyang, China (Peng); Department of Neurology, Taihe Affiliated Hospital of Shiyuan, Shiyuan, China (Ai); Department of Neurology, Sichuan Provincial People's Hospital, Qingyang District, Chengdu, China (F. Guo); Department of Neurology, Zhongnan Hospital of Wuhan University, Wuchang District, Wuhan, China (H. Li); Department of Neurology, Chongqing Three Gorges Central Hospital, Wanzhou District, Chongqing, China (J. Guo); Department of Neurology, The Third Affiliated Hospital of Guangzhou Medical University, Liwan District, Guangzhou, China (Guan); Department of Neurology, Huazhou People's Hospital, Hexi District, Huazhou, China (Zhiyi Wang); Department of Neurology, Lu'an People's Hospital, Jin'an District, Lu'an, China (Y. Liu); Department of Neurology, Hubei Provincial People's Hospital, Wuchang District, Wuhan, China (Pu); Department of Neurology, Changsha Central Hospital, Yuhua District, Changsha, China (Zhen Wang); Department of Neurology, Marcus Stroke & Neuroscience Center, Grady Memorial Hospital, Emory University School of Medicine, Atlanta, Georgia (Nogueira).

Author Contributions: Drs Q. Yang and Nogueira had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Zi and Z. Qiu are co-first authors. Drs Q. Yang and Nogueira are co-corresponding authors.

Concept and design: Zi, Z. Qiu, F. Li, Sang, D. Wu, W. Luo, Shuai, Nogueira, Q. Yang.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: Zi, Z. Qiu, F. Li, Sang, D. Wu, W. Luo, W. Liu, Z. Zhou, Bai, Q. Yang.

Statistical analysis: W. Luo, Shuai Liu, X. Huang.

Obtained funding: Zi, Z. Qiu, F. Li, Sang, Q. Yang.

Administrative, technical, or material support: Zi, Z. Qiu, F. Li, Sang, D. Wu, W. Luo, Shuai Liu, Yuan, Song, Z. Shi, W. Huang, Min Zhang, W. Liu, Z. Guo, T. Qiu, Q. Shi, P. Zhou, L. Wang, Fu, Shudong Liu, S. Yang, S. Zhang, Z. Zhou, X. Huang, Y. Wang, J. Luo, Bai, Min Zhang, Y. Wu, Zeng, Wan, C. Wen, H. Wen, Ling, Z. Chen, Peng, Ai, F. Guo, H. Li, J. Guo, Guan, Zhiyi Wang, Y. Liu, Pu, Zhen Wang, H. Liu, L. Chen, J. Huang, G. Yang, Gong, Shuai, Q. Yang.

Supervision: Zi, Z. Qiu, F. Li, Sang, D. Wu, Shuai, Nogueira, Q. Yang.

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