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Intra-arterial Tenecteplase for Acute Stroke After Successful Endovascular Therapy
The ANGEL-TNK Randomized Clinical Trial

Zhongrong Miao, PhD; Gang Luo, PhD; Ligang Song, MD; Dapeng Sun, PhD; Wenhuo Chen, PhD; Xiaoxi Yao, PhD; Yuesong Pan, PhD; Yaou Liu, PhD; Guangxiong Yuan, MD; Changming Wen, PhD; Ming Wei, MD; Xueli Cai, PhD; Qingcheng Yang, PhD; Zhiming Zhou, MD; Mingze Chang, MD; Guangxian Nan, MD; Jing Wang, MD; Guangyu Xiang, MD; Li Zhou, MD; Wen Gao, MD; Hong Zhang, MD; Jiheng Hao, MD; Chenghua Xu, MD; Yaxuan Sun, MD; Tingyu Yi, MD; Ganghua Feng, MD; Hongxing Han, MD; Feng Gao, PhD; Ning Ma, PhD; Dapeng Mo, PhD; Xuan Sun, PhD; Yiming Deng, PhD; Xu Tong, PhD; Xiaoqing Li, PhD; Baixue Jia, PhD; Bo Wang, PhD; Zijun He, PhD; Ming Yang, PhD; Xingquan Zhao, PhD; Xuelei Zhang, PhD; Longhui Zhang, PhD; Shuo Li, PhD; Xin Tong, PhD; Jing Jing, PhD; Yunyun Xiong, MD; Tao Liu, PhD; Zixiao Li, PhD; Zeguang Ren, MD; Yilong Wang, MD, PhD; David S. Liebeskind, PhD; Tudor G. Jovin, PhD; Thanh N. Nguyen, MD; Yongjun Wang, PhD; Liping Liu, PhD; Bernard Yan, PhD; Xiaochuan Huo, PhD; for the ANGEL-TNK Investigators

IMPORTANCE The role of intra-arterial tenecteplase for acute large vessel occlusion (LVO) stroke after successful endovascular therapy is uncertain.

OBJECTIVE To assess the efficacy and safety of intra-arterial tenecteplase in patients with successful endovascular therapy (defined as a score on the expanded Thrombolysis in Cerebral Infarction [eTICI] scale of 2b to 3) after endovascular therapy.

DESIGN, SETTING, AND PARTICIPANTS This was a prospective, open-label, blinded end point, randomized trial. Recruitment took place between February 16, 2023, and March 23, 2024, with final follow-up on July 4, 2024. The study was conducted across 19 centers in China. Patients with acute anterior circulation LVO treated between 4.5 and 24 hours from the time that the patient was last known to be well were included.

INTERVENTION After successful endovascular recanalization, defined as eTICI 2b or greater, patients were randomized to receive intra-arterial tenecteplase at 0.125 mg/kg (n = 126) or standard medical treatment (n = 129).

MAIN OUTCOMES AND MEASURES The primary end point was excellent outcome at 90 days, defined as modified Rankin Scale (mRS) score of 0 to 1 (range, 0 [no symptoms] to 6 [death]). There were a total of 7 secondary efficacy end points (mRS score of 0-1 at 90 days, mRS score at 90 days, mRS score of 0-2 at 90 days, mRS score of 0-3 at 90 days, National Institutes of Health Stroke Scale score of 0-1 or improved ≥10 points at 36 hours, European Quality of Life Visual Analogue Scale score at 90 days, time to maximum volume > 6 s at 24 hours, and infarct core volume change from baseline) and 3 safety end points, including symptomatic intracranial hemorrhage (sICH) within 48 hours, any intracranial hemorrhage within 48 hours, and all-cause mortality within 90 days.

RESULTS Among 256 patients who were randomized (median [IQR] age, 71.6 [61.3-79.2] years; 113 [44.1%] females), 255 (99.6%) completed the trial. The rate of patients with an mRS score of 0 to 1 at 90 days was 40.5% in the intra-arterial tenecteplase group (n = 51) and 26.4% in the standard medical treatment group (n = 34) (relative risk, 1.44 [95% CI, 1.06-1.95]; *P* = .02). Of 7 prespecified secondary efficacy end points, none showed a significant difference. Intra-arterial tenecteplase after endovascular therapy did not increase the incidence of sICH within 48 hours after treatment compared with standard medical treatment (5.6% vs 6.2%; relative risk, 0.95 [95% CI, 0.36-2.53]; *P* = .92). Mortality at 90 days was 21.4% with intra-arterial tenecteplase and 21.7% with standard medical treatment (relative risk, 0.76 [95% CI, 0.40-1.43]; *P* = .78).

CONCLUSIONS AND RELEVANCE In patients with acute LVO presenting between 4.5 and 24 hours of symptom onset, intra-arterial tenecteplase after successful thrombectomy had a greater likelihood of excellent neurological outcome at 90 days without increasing the risk of sICH or mortality. However, because none of the secondary efficacy analyses supported the primary finding, further trials are needed to confirm the results.

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Visual Abstract

Supplemental content

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

Group Information: A full list of the ANGEL-TNK investigators is provided in Supplement 3.

Corresponding Authors: Xiaochuan Huo, PhD, Department of Cerebral Vascular Disease, Neurological Disease Center, Beijing Anzhen Hospital, Capital Medical University, Beijing, Beijing, China, NO. 2 Anzhen Road, Chaoyang, Beijing, Beijing 100029, China (huoxiaochuan@126.com); Bernard Yan, MD, Department of Neurology at Melbourne Brain Center, The University of Melbourne Medicine at Royal Melbourne Hospital, Neurointervention Service, Royal Melbourne Hospital, Parkville VIC 3050, Australia (bernard.yan@mh.org.au).

Endovascular therapy is an effective treatment for large vessel occlusion (LVO) stroke.[1] However, the rate of poor outcomes remains high after successful recanalization.[2-4] There are several reasons for poor clinical outcomes after successful recanalization, including evolution of cerebral infarction by the time of recanalization, patient comorbidities, and medical complications after stroke.[5] Endovascular recanalization could restore blood flow through the target LVO, but may not lead to adequate reperfusion of distal tissues. Whether intra-arterial thrombolysis after endovascular therapy can improve clinical outcomes by increased reperfusion remains to be explored.

The phase 2b Chemical Optimization of Cerebral Embolectomy (CHOICE) trial showed that among patients with LVO ischemic stroke and successful reperfusion following thrombectomy, the use of adjunct intra-arterial alteplase compared with placebo had a greater likelihood of excellent neurological outcome at 90 days.[6] However, the trial was stopped early and had limitations.[7] On this basis, it was important for these results to be tested in a separate randomized clinical trial.

The Intra-Arterial Recombinant Human TNK-tPA Thrombolysis for Acute LVO After Successful Mechanical Thrombectomy Recanalization (ANGEL-TNK) is an investigator-initiated phase 3 multicenter, randomized, open-label, blinded end point trial. Patients with stroke symptom onset in the past 4.5 hours to 24 hours and who did not receive intravenous thrombolysis on admission were included using computed tomographic (CT) imaging and perfusion imaging screening. The trial investigated whether intra-arterial tenecteplase thrombolysis after successful endovascular therapy of anterior circulation LVO could improve the clinical outcome of patients in a Chinese population.[8]

Key Points

Question In patients with acute large vascular occlusion presenting between 4.5 and 24 hours after symptom onset, does intra-arterial tenecteplase after successful thrombectomy (defined as expanded Thrombolysis in Cerebral Infarction score 2b-3) improve clinical outcomes?

Findings In this randomized clinical trial that included 256 adults, intra-arterial tenecteplase resulted in an excellent functional outcome (modified Rankin Scale score of 0 or 1) in 40.5% patients compared with 26.4% of patients without intra-arterial tenecteplase at 90 days. This difference was statistically significant.

Meaning Among patients with acute large vascular occlusion and successful reperfusion following thrombectomy presenting between 4.5 and 24 hours, adjunct intra-arterial tenecteplase compared with the standard medical treatment group resulted in a greater likelihood of excellent neurological outcome at 90 days.

Methods

Study Design

This multicenter, randomized, open-label, blinded end point clinical trial was conducted at 19 comprehensive stroke center hospitals in China. Details of the rationale, design, and methods of the trial have been previously reported.[8] The trial was approved by the ethics committee at Beijing Tiantan Hospital (approval No. KY2020-170-02) and all participating centers. Written informed consent was obtained by each patient or their authorized representative. The full protocol and statistical analysis plan are available in Supplement 1. The steering committee designed, conducted, and analyzed the trial data. An imaging core laboratory centrally adjudicated all images. A data and safety monitoring committee monitored the trial, with regular assessment of safety outcomes. The statistical and data management center in the China National Clinical Research Center for Neurological Diseases conducted the analysis. The trial was conducted in accordance with the Declaration of Helsinki Harmonization Guidelines. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Study Participants

Eligible patients were 18 years or older with time last known well to randomization of 4.5 to 24 hours. Patients had National Institutes of Health Stroke Scale (NIHSS) score of greater than or equal to 2 (range, 0 to 42; higher scores indicate greater neurological deficit), had a prestroke score of 0 or 1 on the modified Rankin Scale (mRS; range, 0 to 6; higher scores indicate increasing disability, with 6 indicating death) before stroke onset, and signed informed consent from the patient or their health care proxy. Regarding ethnicity, we aimed to understand the potential confounding effects on study outcomes. Participants or their authorized representative were provided with fixed categories to report their ethnicity. Imaging inclusion criteria were intracranial occlusion of the internal carotid artery (ICA) shown on CT angiography (CTA) or magnetic resonance angiography (MRA) or M1 or dominant M2 segment of the middle cerebral artery (MCA); Alberta Stroke Program Early CT Score (ASPECTS) greater than or equal to 6 on noncontrast CT scan or diffusion-weighted imaging MRI; ischemic infarct core less than 70 mL, mismatch ratio greater than or equal to 1.2, and mismatch volume greater than or equal to 10 mL on CT perfusion or MR perfusion; and treated with endovascular therapy resulting in an expanded Thrombolysis in Cerebral Infarction (eTICI) score of 2b50 to 3 at the end of the procedure.

Patients who received intravenous thrombolysis on admission, received intravenous heparin during treatment, or would likely require antiplatelet therapy within the first 24 hours after endovascular treatment were excluded from enrollment. Patients were ineligible if they had midline shift or clinical signs of herniation, mass effect, high risk of hemorrhage, acute bilateral strokes, or multiple intracranial occlusions. Additional inclusion and exclusion criteria are provided in the protocol (Supplement 1).[8]

Randomization and Intervention Procedures

Randomization was generated by a 24-hour real-time central network system. The investigator in each center obtained a code from the randomization system according to the enrollment order, and eligible participants were randomized in a 1:1 ratio to receive intra-arterial tenecteplase (intra-arterial tenecteplase group) or standard medical management (medical

treatment group) according to the block method (4 cases/block) to ensure balance between and within the groups. Randomization was done after successful endovascular therapy (eTICI score 2b50-3) stratified by center and initial occlusion site on digital subtraction angiography.

Medical management in both groups followed the Chinese Stroke Association guidelines.[9] For patients randomized to the intra-arterial tenecteplase group, recombinant human tenecteplase tissue-type plasminogen activator (rhTNK-tPA) 0.125 mg/kg with maximum dose of 12.5 mg was infused slowly and constantly over 15 minutes. Administration of rhTNK-tPA was through a microcatheter in the horizontal segment of the middle cerebral artery distal to the origin of the lenticulostriate branches. At the end of the intra-arterial infusion, anteroposterior and lateral angiography were performed to record the final eTICI grading. For patients randomized to the standard medical treatment group, the procedure terminated after additional control follow-up angiography.

Outcomes

The Rankin Structured Interview[10] was used as scoring tool to assess the 90-day mRS (range, 0 [no symptoms] to 6 [death] for evaluation of neurological functional disability). The primary outcome was excellent outcome, defined as mRS score of 0 to 1 at 90 days. Secondary outcomes included 90-day mRS score (shift analysis); 90-day mRS score of 0 to 2 and 0 to 3 (mRS score of 0-1 = nondisabled; mRS 0-2 = functionally independent; mRS 0-3 = ambulatory and self-care capable); NIHSS score of 0 to 1 or an improvement in NIHSS score of at least 10 points at 36 hours after randomization; critically hypoperfused tissue volume (CT perfusion voxels with time to reach the maximum of the tissue residue function, time to maximum volume > 6 s) at 24 hours; infarct core volume change from baseline imaging (calculated by CT perfusion or diffusion-weighted imaging) to noncontrast CT imaging at 7 days or at discharge (whichever is earlier) or MRI at 36 hours; and 90-day European Quality of Life Visual Analogue Scale (EQ-VAS; range, 0-100; lower scores indicate worse quality of life). Safety outcomes were symptomatic intracranial hemorrhage within 48 hours after randomization defined by the Heidelberg bleeding classification (an increase of ≥4 points or an increase of ≥2 points of an NIHSS subcategory is a relevant change in neurological status with any intracranial hemorrhage on imaging),[11] any intracranial hemorrhage within 48 hours of randomization, and death within 90 days after stroke onset. The mRS score was assessed through telephone interviews with recording for quality control at 90 days by 2 independent trained neurologists who were unaware of trial group assignment. All adverse events were confirmed by a clinical event adjudication committee masked to the trial group assignments. Further definitions of outcomes are included in the protocol.

Imaging Assessments

Imaging was performed at baseline, 36 (±12) hours and 7 (±1) days after randomization, or at discharge. All imaging data were submitted to the imaging core laboratory for independent adjudication of the baseline ASPECTS, site of arterial occlusion, reperfusion, and follow-up intracranial hemorrhage. Site and central coordinator clinicians conducted real-time online imaging evaluation to ensure the accuracy of imaging assessments (Supplement 1). The infarct core was evaluated by the iStroke software (research version provided by Beijing Tiantan Hospital and Biomind free of charge to trial centers) and defined as relative cerebral blood flow less than 30% based on CT perfusion or apparent diffusion coefficient less than 620×10^{-6} mm^2/s based on MRI.[12]

Reperfusion was measured with the eTICI (7-point scale with higher scores indicating greater reperfusion) and successful reperfusion was defined as eTICI 2b50 or greater, which indicates 50% to 66% reperfusion or more of the affected territory.

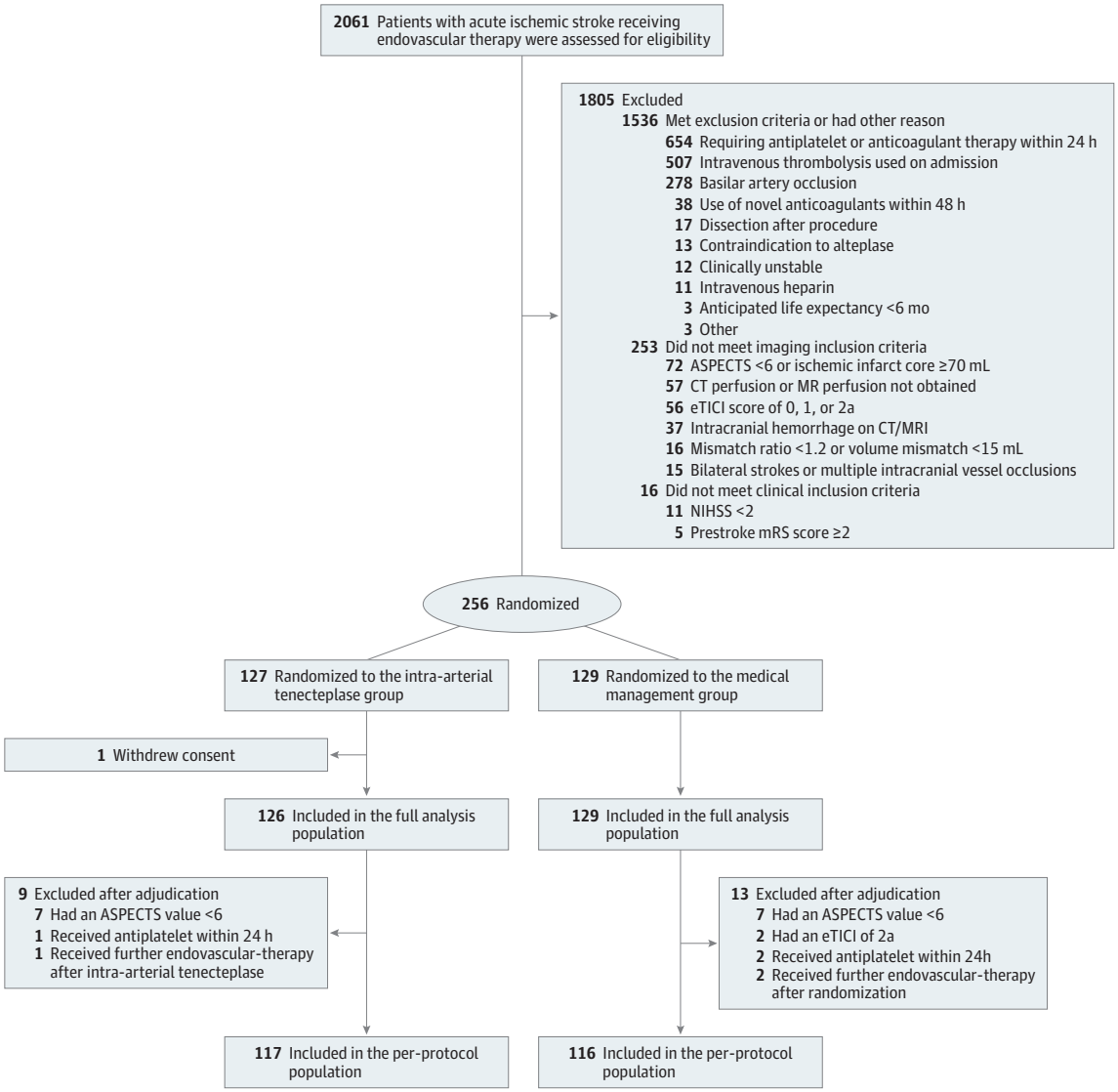
Sample Size Calculation

According to data from the CHOICE trial,[6] we assumed a rate of 40% for mRS score of 0 or 1 in the control group of patients with LVO, a 19% improvement in the experimental group with 80% statistical power, and a 5% 2-sided type I error and 5% loss to follow-up. Therefore, 256 patients were required for the sample size, with 128 patients in each group. An interim analysis was conducted when the 90-day follow-up of half of the total sample size was completed. The corresponding significance levels based on the O'Brien-Fleming boundary were 2-sided *P* values of .003 (interim analysis) and .049 (final analysis).

Statistical Analysis

Patients were analyzed according to their randomization group. All randomized patients with completed 3-month outcome assessments were included in the full analysis set. The primary efficacy end point analysis of this study was performed on the full analysis set. For the primary efficacy end point, complete data were used and missing data were not imputed in the main analysis. For secondary outcomes, only complete data were used for analysis. We did not account for multiple comparisons of the secondary end points and, as such, these findings should be interpreted as exploratory. Sensitivity analyses were conducted in the per-protocol population. For the primary outcome, a generalized linear model with log link and binomial error distribution with adjustment for study center and occlusion site was used to calculate the relative risk (RR) and 95% CI between the 2 treatment groups. Similar models were used for the secondary outcomes of mRS score of 0 to 2 at 90 days, mRS score of 0 to 3 at 90 days, NIHSS of 0 or 1 or improved at least 10 points at 24 hours, and bleeding events within 48 hours. Wilcoxon-Mann-Whitney generalized odds ratio with 95% CI was calculated to compare the distribution of mRS score at 90 days because the proportional odds assumption for ordinal logistic regression was not met ($P < .001$). A linear mixed model with adjustment for study center and occlusion site was used to compare the time to maximum volume greater than 6 seconds at 24 hours, 24-hour infarct core volume change from baseline, and EQ-VAS at 90 days between the 2 treatment groups. The Cox proportional hazard model with site as a random effect was used to compare the risk of death within 90 days between the 2 treatment groups and the hazard ratio with its 95% CI was calculated. Summary tables were produced for

Figure 1. Enrollment and Randomization of Patients



eTICI indicates expanded Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale. Modified Rankin Scale (mRS) scores range from 0 to 6, with higher scores indicating greater disability. The Alberta Stroke Program Early Computed Tomographic Score (ASPECTS) ranges from 0 to 10, with lower scores indicating larger infarction.

the predefined subgroups and interactions between treatment and these subgroups used generalized linear models. A separate model was used for each interaction to determine its significance. The primary outcome was 2-sided with $P < .049$ considered significant and all other statistics were 2-sided with $P < .05$ considered significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc).

Results

Patient Population

Between February 16, 2023, and March 23, 2024, a total of 2061 patients were screened at 19 centers, of whom 256 patients (12.4%) were enrolled, with 126 randomized to the intra-arterial tenecteplase group and 129 were randomized to the standard medical treatment group (**Figure 1**; eFigures 1 and 2 in Supplement 2). The main reasons for nonenrollment were intravenous thrombolysis use at admission (n = 507), basilar artery occlusion (n = 278), and angioplasty, stent, or other conditions that would require antiplatelet or anticoagulant therapy within 24 hours of admission (n = 654) (eTable 1 in Supplement 2). One patient, whose representative withdrew consent immediately after randomization and was randomized to the intra-arterial tenecteplase group, was not included in the intention-to-treat analysis. There was no crossover between the groups. All patients randomized to the intervention group received the full dose of intra-arterial tenecteplase.

Of the 255 patients, 55 (27 in the intra-arterial tenecteplase and 28 in the standard medical treatment group) died before 90 days. No patient had missing data regarding the primary outcome. A total of 22 patients (9 in the intra-arterial tenecteplase and 13 in the standard medical treatment group) were excluded from the per-protocol analysis because, on review, they had an ineligible baseline ASPECTS value, eTICI score, or antiplatelet strategy or because they received further endovascular therapy after randomization (Figure 1).

The baseline demographic and clinical characteristics of patients were similar between the 2 groups (**Table 1**; eTable 2 in Supplement). The median (IQR) age of participants was 71.6 (61.3-79.2) years, and 114 (44.7%) were females. Ethnicity included patients mainly from the Han region, but included small numbers of participants from Miao (0.8%) and Zhuang (0.8%) regions (eTable 2 in Supplement 2). The median (IQR) NIHSS was 15.0 (12.0-19.0), ASPECTS was 7.0 (6.0-8.0), and infarct volume was 19.0 (4.0-45.6) mL on admission. Sixteen patients were considered misclassified after adjudication by the core laboratory (14 on ASPECTS and 2 on eTICI). Occlusions of the internal carotid artery occurred in 33 participants (26.2%) in the tenecteplase group and 38 (29.5%) in the standard medical treatment group; ipsilateral extracranial internal carotid artery occlusion was present in 1 patient (0.8%) in each group. The median (IQR) interval between stroke onset and randomization was 9.38 (6.53-13.05) hours. The follow-up angiogram showed that eTICI score improved after intra-arterial thrombolysis (eTable 4 in Supplement 2). Other concomitant treatment and details of endovascular therapy are reported in eTable 3 and 4 in Supplement 2, respectively.

Primary and Secondary Outcomes

Intra-arterial tenecteplase after endovascular therapy resulted in a higher percentage of patients with an mRS score of 0 or 1 at 90 days than standard medical treatment (51 [40.5%] vs 34 [26.4%]; RR, 1.44 [95% CI, 1.06-1.95]; P = .02) (**Figure 2** and **Table 2**). For secondary outcomes, the median (IQR) 90-day mRS score was 3 (1-5) in the intra-arterial tenecteplase group and 3 (1-4) in the standard medical treatment group (crude odds ratio, 1.13 [95% CI, 0.84-1.52]). The percentage of patients with an mRS score of 0 to 2 at 90 days was 46.0% (n = 58) in the intra-arterial tenecteplase group and 46.5% (n = 60) in the standard medical treatment group (RR, 0.94 [95% CI, 0.74-1.20]). The percentage of patients with an mRS score of 0 to 3 at 90 days was 53.2% (n = 67) in the intra-arterial tenecteplase group and 55.8% (n = 72) in the standard medical treatment group (RR, 0.92 [95% CI, 0.73-1.15]). The percentage of patients with an NIHSS score of 0 to 1 or an improvement in NIHSS of at least 10 points at 36 hours after randomization was 13.5% (n = 17) in the intra-arterial tenecteplase group and 15.5% (n = 20) in the standard medical treatment group (RR, 0.84 [95% CI, 0.53-1.36]). The median (IQR) 90-day EQ-VAS score was 75 (40.0-95.0) in the intra-arterial tenecteplase group and 70 (25-90) in the standard medical treatment group (β, 4.11 [95% CI, −5.18 to 13.40]). The efficacy for the primary outcome is shown in predefined subgroups (**Figure 3**). In the subgroup analyses, intra-arterial tenecteplase also significantly improved the prognosis in

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline[a]

Variable	Intra-arterial tenecteplase (n = 126)	Standard medical treatment (n = 129)
Age, median (IQR), y	71.5 (60.6-79.5)	71.7 (61.7-79.0)
Sex, No. (%)		
Female	58 (46.0)	56 (43.4)
Male	68 (54.0)	73 (56.6)
Stroke classification, No. (%)		
Cardioembolic	89 (70.6)	83 (64.3)
Atherothrombotic	30 (23.8)	37 (28.7)
Undetermined and others	7 (5.6)	9 (7.0)
Baseline modified Rankin Scale score of 1, No. (%)	8 (6.3)	11 (8.5)
NIHSS score at admission, median (IQR)[b]	15 (12-19)	16 (12-19)
Occlusion site, No. (%)[c]		
Intracranial internal carotid artery	33 (26.2)	38 (29.5)
M1 middle cerebral artery segment	58 (46.0)	64 (49.6)
M2 middle cerebral artery segment	35 (27.8)	27 (20.9)
Ipsilateral extracranial internal carotid artery stenoocclusion, No. (%)[d]	1 (0.8)	1 (0.8)
Clot Burden Score, median (IQR)	6.00 (4.00-9.00)	6.00 (4.00-7.00)
ASPECTS value based on CT, median (IQR)[e]	7.00 (6.00-8.00)	7.00 (6.00-8.00)
Collateral grade, No. (%)[f]		
0 (Absent collateral filling)	9 (7.1)	9 (7.0)
1 (Filling ≤50%, but >0%)	60 (47.6)	42 (32.6)
2 (Filling >50%, but <100%)	50 (39.7)	64 (49.6)
3 (Filling 100%)	7 (5.6)	14 (10.9)
Systolic blood pressure at hospital arrival, median (IQR), mm Hg	139.00 (125.00-160.00)	137.00 (125.00-158.00)
Glucose level at hospital arrival, median (IQR), mg/dL	127 (110-146)	128 (111-155)
Unwitnessed stroke, No. (%)	73 (57.9)	64 (49.6)
Baseline infarct volume, median (IQR), ml[g]	19.83 (3.80-39.90)	18.10 (4.30-51.00)
ASTIN/SIR collateral score, median (IQR)	1.00 (1.00-2.00)	1.00 (1.00-2.00)
Passes, No. (%)		
1	72 (57.1)	69 (53.5)
2	36 (28.6)	36 (27.9)
≥3	18 (14.3)	24 (18.6)
First-pass success, No. (%)[h]	46 (36.5)	60 (46.5)
Angiographic eTICI scores at randomization, No. (%)[i]	n = 126	n = 127
2b50: 50%-66% Reperfusion	38 (30.2)	33 (25.6)
2b67: 67%-89% Reperfusion	49 (38.9)	44 (34.1)
2c: 90%-99% Reperfusion	28 (22.2)	38 (29.5)
3: 100% Reperfusion	11 (8.7)	12 (9.3)
Interval between time of stroke onset and puncture time, median (IQR), h	7.83 (5.5-12.3)	8.3 (5.7-12.2)

(continued)

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline[a] (continued)

Variable	Intra-arterial tenecteplase (n = 126)	Standard medical treatment (n = 129)
Interval between time of stroke onset and time of reperfusion, median (IQR), h	9.05 (6.6-13.3)	9.3 (6.7-12.9)
Interval between time of stroke onset and time of randomization, median (IQR), h	9.31 (6.7-13.5)	9.5 (6.9-13.0)
4.5-6	24 (19.0)	25 (19.4)
6-12	61 (48.4)	64 (49.6)
12-24	41 (32.5)	40 (31.0)
Interval between time of stroke onset and intra-arterial tenecteplase, median (IQR), h	9.4 (6.7-13.8)	

Abbreviation: eTICI, expanded Thrombolysis in Cerebral Infarction.

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

[a] Percentages may not total 100 because of rounding.

[b] Scores on the National Institutes of Health Stroke Scale (NIHSS), an ordinal scale that is used to evaluate the severity of stroke, range from 0 to 42, with higher scores indicating greater neurological deficit.

[c] The M1 segment is the main trunk of the middle cerebral artery, and the M2 segment is the first-order branch of the main trunk of the middle cerebral artery.

[d] The entry Ipsilateral Carotid artery occlusion is defined as a severe stenosis or occlusion of the extracranial internal carotid artery ipsilateral to its intracranial occlusion.

[e] Alberta Stroke Program Early Computed Tomography Score (ASPECTS) values range from 0 to 10, with lower values indicating larger infarction.

[f] Collateral filling in the middle cerebral artery territory of the affected hemisphere is expressed as a percentage of the collateral filling in the contralateral middle cerebral artery territory. MRA was performed in 13 cases without CTA collateral evaluation.

[g] Infarct core volume was assessed with the use of the apparent diffusion coefficient values based on MRI in 13 patients; the relative cerebral blood flow based on CT perfusion was used to assess infarct-core volume in the other patients. The infarct core was defined as an area with a relative cerebral blood flow of less than 30% based on CT perfusion imaging or an apparent diffusion coefficient value of less than 620 × 10 − 6 mm^2 per second on the basis of MRI.

[h] The first-pass effect is defined as achieving a complete recanalization (eTICI 3) with a single thrombectomy device pass.

[i] Two patients in control group with an eTICI of 2a were excluded from per-protocol population after adjudication by imaging core laboratory.

individuals with higher blood glucose levels (≥100 mg/dL) (RR, 1.82 [95% CI, 1.35-2.46]; $P < .001$), and there was an interaction effect compared with the strata of individuals with lower blood glucose levels (<100 mg/dL) ($P = .02$). The primary and secondary outcome results of the per-protocol analysis were similar to the intention-to-treat analyses (eFigure 3 and eTable 5 in Supplement 2).

Adverse Events

Symptomatic intracranial hemorrhage within 48 hours from randomization occurred in 7 patients (5.6%) in the intra-arterial tenecteplase group and in 8 patients (6.0%) in the standard medical treatment group (RR, 0.95 [95% CI, 0.36-2.53]; $P = .92$) (Table 2). Any intracranial hemorrhage within 48 hours occurred in 31 patients (24.6%) in the intra-arterial tenecteplase group and in 36 patients (27.9%) in the standard medical treatment group (RR, 0.90 [95% CI, 0.59-1.37]; $P = .63$). The rate of death within 90 days was 21.4% in the intra-arterial tenecteplase group and 21.7% in the standard medical treatment group. Other serious adverse events occurred in 20 patients (15.9%) in the intra-arterial tenecteplase group and 18 patients (13.9%) in the standard medical treatment group.

Discussion

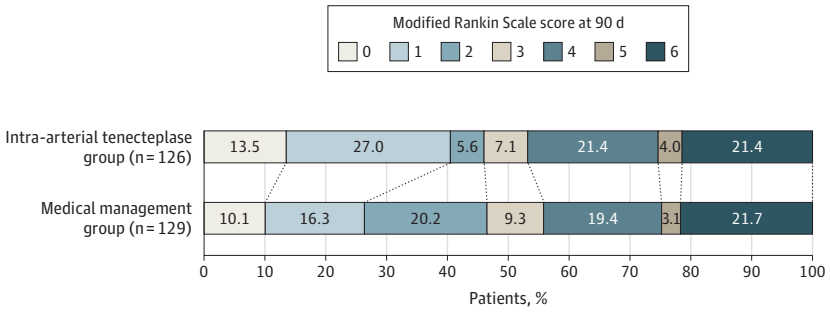
In this open-label, blinded end point, randomized trial of patients with acute anterior circulation LVO presenting 4.5 to 24 hours from stroke onset, intra-arterial tenecteplase after successful endovascular treatment resulted in a higher percentage of patients with excellent neurological outcome (modified Rankin Scale score of 0 or 1) at 90 days than standard medical treatment. There was no significant difference in symptomatic intracranial hemorrhage within the first 48 hours after treatment and 90-day mortality between the 2 groups.

The primary outcome of 90-day mRS score of 0 to 1 was chosen because it was assumed that lytic benefit added to the already substantial benefit of endovascular therapy would cluster toward very favorable outcomes at the mRS score of 0 to 1 vs 2 to 6. Therefore, dichotomization of mRS score in lieu of ordinal shift analysis was used as the primary outcome.[13] The baseline ASPECTS was low in the current trial compared with many thrombectomy trials, which may explain the lower proportion of patients achieving an mRS scores of 0 to 1 in the standard medical treatment group. Intra-arterial administration of tenecteplase may enhance microvascular reperfusion, allowing blood flow to reach viable tissues within the radiologically defined infarcted zones and thereby conferring clinical benefit. Secondary analyses (using different thresholds or a shift analysis) of the mRS end point yielded results that were not statistically significant.

Building on previous clinical experience, the ANGEL-TNK trial restricted the use of periprocedural antithrombotic drugs via defined inclusion and exclusion criteria. With these measures in place to reduce risk of intracranial hemorrhage, a higher intra-arterial tenecteplase dose (0.125 mg/kg) was administered in the current trial compared with other trials, which used half the dosage of intravenous thrombolysis.[8] To decrease the potential bleeding risk associated with intra-arterial thrombolysis after thrombectomy, there were several additional restrictions in the current trial's eligibility criteria. Patients presenting between 4.5 to 24 hours after symptom onset were included because these patients were not considered eligible for intravenous thrombolysis according to Chinese guidelines.[14] Patients who required antiplatelet therapy or anticoagulation within the first 24 hours and intravenous heparin administration during endovascular treatment (heparinized saline flushes were allowed) were also not included in this trial.[8] The concern for higher bleeding risk was confirmed by the MR CLEAN Med trial results, which showed a higher risk of symptomatic intracranial hemorrhage in patients who received periprocedural intravenous aspirin and unfractionated heparin during endovascular stroke treatment.[15]

The results of the current study align with several trials. The CHOICE trial showed that among patients with anterior

Figure 2. Distribution of the 90-Day Modified Rankin Scale Score in Patients Presenting Within 24 Hours of Symptom Onset



Scores range from 0 to 6, with 0 indicating no symptoms; 1, no clinically significant disability; 2, slight disability (the patient is able to look after their own affairs without assistance but unable to carry out all previous activities); 3, moderate disability (patient requires some help but is able to walk unassisted); 4, moderately severe disability (patient is unable to attend to bodily needs without assistance and unable to walk unassisted); 5, severe disability (patient requires constant nursing care and attention); and 6, death.

Table 2. Trial Outcomes

Variable	Intra-arterial tenecteplase (n = 126)	Standard medical treatment (n = 129)	Treatment effect (95% CI)	*P* value
Primary outcome				
Modified Rankin Scale score of 0 to 1 at 90 d, No. (%)	51 (40.5)	34 (26.4)	RR: 1.44 (1.06 to 1.95) RD: 13.27 (3.24 to 23.29)	.02
Secondary outcome				
Modified Rankin Scale score at 90 d, median (IQR)	3 (1-5)	3 (1-4)	OR: 1.13 (0.84 to 1.52)	.41
Modified Rankin Scale score o f 0 to 2 at 90 d, No. (%)	58 (46.0)	60 (46.5)	RR: 0.94 (0.74 to 1.20) RD: −1.42 (−12.34 to 9.50)	.63
Modified Rankin Scale score of 0 to 3 at 90 d, No. (%)	67 (53.2)	72 (55.8)	RR: 0.92 (0.73 to 1.15) RD: −4.21 (−15.75 to 7.33)	.45
NIHSS 0-1 or improved ≥10 points at 36 h, No. (%)[a]	17 (13.5)	20 (15.5)	RR: 0.84 (0.53 to 1.36) RD: −1.89 (−9.09 to 5.32)	.49
European Quality of Life Visual Analogue Scale score at 90 d, median (IQR)	75.00 (40.00-95.00)	70.00 (25.00-90.00)	MD: 4.11 (−5.18 to 13.40)	.38
Time to maximum volume >6 s at 24 h, median (IQR)[b]	0.00 (0.00-28.70)	4.50 (0.00-46.20)	MD: −9.08 (−31.15 to 12.98)	.42
Infarct core volume change from baseline, median (IQR)[c]	−11.30 (−37.00 to 0.00)	−8.00 (−28.50 to 0.00)	MD: −0.32 (−8.96 to 8.31)	.94
Safety outcomes, No. (%)				
Symptomatic intracranial hemorrhage within 48 h[d]	7 (5.6)	8 (6.2)	RR: 0.95 (0.36 to 2.53) RD: −1.84 (−7.59 to 3.91)	.92
Any intracranial hemorrhage within 48 h	31 (24.6)	36 (27.9)	RR: 0.90 (0.59 to 1.37) RD: −2.09 (−12.19 to 8.01)	.63
Death within 90 d	27 (21.4)	28 (21.7)	RR: 0.76 (0.40 to 1.43) RD: 0.76 (−7.20 to 8.72)	.78

Abbreviations: MD, mean difference; OR, odds ratio; RD, risk difference; RR, risk ratio.

[a] The National Institutes of Health Stroke Scale (NIHSS) score is an ordinal scale to evaluate the severity of stroke ranged from 0 to 42, with higher scores indicating a more severe deficit. Data were missing for 1 patient in standard medical treatment group because of early discharge.

[b] There were 83 patients who could not be assessed with perfusion because of unsuitable clinical practice (34 in the intra-arterial tenecteplase group and 49 in the standard medical treatment group).

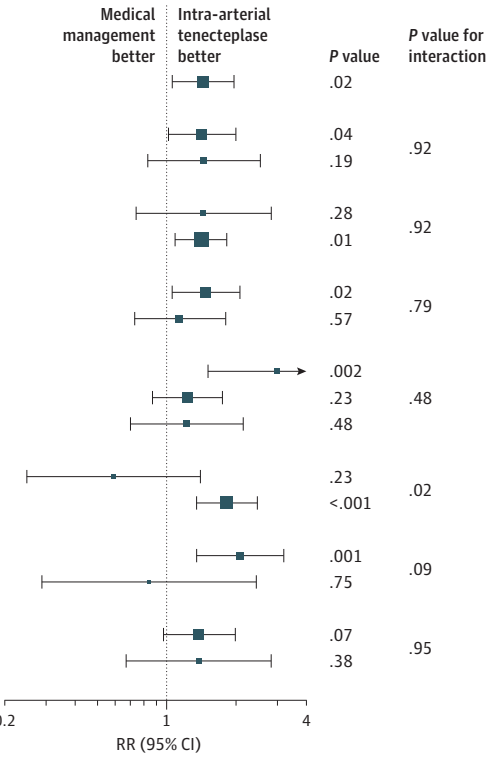
[c] Infarct core volume change from baseline imaging (calculated by computed tomographic perfusion or diffusion-weighted imaging) to noncontrast computed tomographic scan at 7 days or at discharge (whichever is earlier), or magnetic resonance imaging at 36 hours. There were 2 patients who could not be assessed because of serious illness or death (both in the medical-management group).

[d] Symptomatic intracranial hemorrhage was defined according to the Heidelberg bleeding classification (an increase in the NIHSS score of ≥4 points or an increase in the score for an NIHSS subcategory of ≥2 points with any intracranial hemorrhage on imaging).[11]

LVO acute ischemic stroke and successful reperfusion following thrombectomy (eTICI 2b to 3), the use of adjunct intra-arterial alteplase resulted in a greater likelihood of excellent neurological outcome at 90 days.[6] However, the results of this trial were limited by its small sample size related to premature stopping of the trial.[7] The prospective ALLY pilot trial showed that adjunct intra-arterial tenecteplase up to 4.5 mg in patients with incomplete reperfusion after endovascular therapy was feasible and not associated with increased rates of hemorrhage.[16] Preliminary results of the PEARL trial, also

Figure 3. Analyses of the Primary Outcome According to Prespecified Subgroups

Subgroup	No. of patients with event/total No.		RR (95% CI)	P value	P value for interaction
	Intra-arterial tenecteplase group	Medical management group			
Overall	51/126 (40.5)	34/129 (26.4)	1.44 (1.06-1.95)	.02	
Age, y					
18-65	20/39 (51.3)	14/45 (31.1)	1.42 (1.02-1.99)	.04	.92
≥66	31/87 (35.6)	20/84 (23.8)	1.45 (0.83-2.54)	.19	
Time last known to be well to randomization, h					
4.5-6	11/24 (45.8)	8/25 (32.0)	1.44 (0.74-2.83)	.28	.92
6-24	40/102 (39.2)	26/104 (25.0)	1.41 (1.09-1.82)	.01	
Stroke severity before randomization					
NIHSS <16	38/71 (53.5)	23/63 (36.5)	1.48 (1.06-2.07)	.02	.79
NIHSS ≥16	13/55 (23.6)	11/66 (16.7)	1.14 (0.73-1.80)	.57	
Occlusion site					
ICA	13/33 (39.4)	5/38 (13.2)	2.99 (1.51-5.96)	.002	
M1	19/58 (32.8)	17/64 (26.6)	1.23 (0.87-1.74)	.23	.48
M2	19/35 (54.3)	12/27 (44.4)	1.22 (0.70-2.14)	.48	
Admission serum glucose level, mg/dL					
<100	4/15 (26.7)	10/19 (52.6)	0.59 (0.25-1.40)	.23	.02
≥100	47/111 (42.3)	24/110 (21.8)	1.82 (1.35-2.46)	<.001	
Randomization eTICI					
eTICI 2b	39/87 (44.8)	15/77 (19.5)	2.08 (1.35-3.20)	.001	.09
eTICI 2c/3	12/39 (30.8)	19/50 (38.0)	0.84 (0.29-2.44)	.75	
Stroke type					
Cardiac embolism	38/89 (42.7)	23/83 (27.0)	1.38 (0.97-1.98)	.07	.95
Large-artery atherosclerosis	10/30 (33.3)	9/37 (24.3)	1.38 (0.67-2.82)	.38	



ASPECTS indicates Alberta Stroke Program Early Computed Tomographic Score; eTICI, expanded Thrombolysis in Cerebral Infarction; ICA, intracranial internal carotid artery; NIHSS, National Institutes of Health Stroke Scale. The M1 segment is the main trunk of the middle cerebral artery, M2 segment is the first-order branch of the main trunk. The area of the black squares is proportional to the sample size.

including patients with anterior LVO acute stroke and successful reperfusion after endovascular therapy (eTICI 2b to 3), showed higher likelihood of mRS scores of 0 to 1 at 90 days with intra-arterial alteplase 0.225 mg/kg compared with standard care (44.8% vs 30.2%; RR, 1.45 [95% CI, 1.08-1.96]; $P = .01$).[17]

In contrast, the ATTENTION-IA trial showed that intra-arterial tenecteplase after successful endovascular recanalization of the posterior circulation did not improve 90-day excellent functional outcomes compared with successful endovascular recanalization alone.[18] Symptomatic intracranial hemorrhage was numerically higher in patients receiving intra-arterial tenecteplase. Because the ATTENTION-IA trial did not exclude patients who had received intravenous thrombolysis or who would require antiplatelet therapy with angioplasty or stenting, it is possible that this may have accounted for the higher bleeding risk seen with intra-arterial tenecteplase in their trial.

Moreover, 2 trials (POST-UK and POST-TNK) showed that adjunctive intra-arterial tenecteplase or urokinase following near-complete to complete reperfusion (eTICI 2c to 3) by endovascular thrombectomy did not significantly increase the likelihood of freedom from disability,[19,20] despite point estimates favoring the intra-arterial thrombolytic group with a 5% effect size in both the POST-UK and POST-TNK trials. The current trial was different from these 2 trials in that the use of antiplatelets was not allowed during thrombectomy or within 24 hours after thrombectomy in ANGEL-TNK. This may explain why ANGEL-TNK included more patients with cardiac embolism (70.6% vs 64.3% in the intervention vs control group) compared with the POST-UK (38.6% vs 39.7%) and POST-TNK (50.2% vs 50.6%) trials. Acute antiplatelet therapy (eg, tirofiban) may have attenuated the treatment effect with intra-arterial tenecteplase or increased the bleeding risk.

Of note, the current study included the same population of patients who underwent successful recanalization (eTICI 2b-3; 50%-100% reperfusion) after endovascular therapy as the CHOICE and PEARL trials.[6,8,17] However, the POST-UK and POST-TNK trials excluded patients with eTICI 2b50-67 (50%-89% reperfusion). Among patients enrolled in the current trial, 64.3% of patients (164/255) had an eTICI of 2b50 (50%-66% reperfusion). The benefit seen in the current trial for intra-arterial thrombolysis among patients with new or residual distal medium vessel occlusions (50%-89% reperfusion for those with eTICI of 2b5-67) after successful mechanical recanalization of large vessel target lesions suggests that intra-arterial thrombolysis is also a promising strategy to investigate in patients presenting with spontaneous, isolated, distal medium vessel occlusions. Previous studies suggested that patients who achieve macroscopic angiographic recanalization may not have reperfusion of the brain tissue.[6,21] However, the POST-UK and POST-TNK trials suggested that patients who achieved

complete reperfusion of all macroscopically visible vessels may not benefit from intra-arterial thrombolytics targeting microcirculatory thrombosis.

In contrast with recent studies,[18,19] the current trial conducted a follow-up angiogram after intra-arterial thrombolysis and the standard medical treatment group also underwent angiographic evaluation after randomization. The follow-up angiogram showed that eTICI score improved after intra-arterial thrombolysis (eTable 4 in Supplement 2). This observation suggests that the benefit of intra-arterial thrombolysis might be attributed to the treatment of residual macrovascular occlusions, and this might also be the reason that this trial was able to demonstrate an improvement in patient outcomes in contrast with the POST-UK and POST-TNK trials.

Limitations

This study has several limitations. First, patients who received intravenous thrombolysis, periprocedural intravenous heparin, or antiplatelet use were not included, affecting the generalizability of the trial results. Second, the intra-arterial tenecteplase dose was based on previous clinical experience; whether lower doses are as effective remains to be studied. Third, those who needed glycoprotein IIb/IIIa inhibitors were excluded, so the population was primarily individuals with cardioembolic stroke. The results need to be further verified by other trials.

Conclusions

Among patients with acute LVO presenting between 4.5 and 24 hours from symptom onset and who had successful recanalization, adjunct intra-arterial tenecteplase resulted in a greater likelihood of excellent neurological outcome at 90 days compared with standard medical care. The risk of intracranial hemorrhage was similar between the groups. However, because none of the secondary efficacy analyses supported the primary finding, further trials are needed to confirm the results.

ARTICLE INFORMATION

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Author Affiliations: Interventional Neuroradiology, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, Beijing, China (Miao, Luo, Song, D. Sun, F. Gao, Ma, Mo, X. Sun, Deng, Xu Tong, X. Li, Jia, B. Wang, He, M. Yang, L. Zhang); Department of Cerebral Vascular Disease, Neurological Disease Center, Beijing Anzhen Hospital, Capital Medical University, Beijing, Beijing, China (Miao, X. Zhang, S. Li, Xin Tong, Huo); Department of Neurology, Fujian Medical University Union Hospital, Fuzhou, Fujian, China (Chen); Department of Neurology, The First People's Hospital of Chenzhou, Chenzhou, Hunan, China (Yao); China National Clinical Research Center for Neurological Diseases, Beijing, Beijing, China (Pan, Zhao, Jing, Xiong, Z. Li, Yilong Wang, Yongjun Wang, L. Liu); Beijing Institute for Brain Disorders, Capital Medical University, Beijing, Beijing, China (Pan, Zhao, Jing, Xiong, Z. Li, Ren, Yilong Wang, Yongjun Wang, L. Liu); Department of Radiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, Beijing, China (Y. Liu); Department of Emergency, Xiangtan Central Hospital, Xiangtan, Hunan, China (Yuan); Department of Neurology, Nanyang Central Hospital, Nanyang, Henan, China (Wen); Department of Neurosurgery, Tianjin huanhu hospital, Tianjin, Tianjin, China (Wei); Department of Neurology, The Municipal Central Hospital of Lishui, Lishui, Zhejiang, China (Cai); Department of Neurology, Anyang People's Hospital, Henan, Anyang, China (Q. Yang); Department of Neurology, Yijishan Hospital of Wannan Medical College, Wuhu, Anhui, China (Z. Zhou); Department of Neurology, Xi'an No.3 Hospital, Xi'an, Shanxi, China (Chang); Department of Neurology, China-Japan Union Hospital of Jilin University, Changchun, Jilin, China (Nan); Neurointerventional Radiology, Beijing Fengtai You'anmen Hospital, Beijing, Beijing, China (J. Wang); Department of Neurology, Xuchang Central Hospital, Xuchang, Henan, China (Xiang); Department of Neurology, Weifang peoples' Hospital, Weifang, Shandong, China (L. Zhou); Department of Neurology, Liuzhou People's Hospital Affiliated to Guangxi Medical University, Liuzhou, Guangxi, China (W. Gao); Department of Neurology, General Hospital of Fushun Mining Bureau of Liaoning Health Industry Group, Fushun, Liaoning, China (H. Zhang); Department of Neurosurgery, Liaocheng People's Hospital, Liaocheng, Shandong, China (Hao); Department of Neurology, Huangyan Hospital of Wenzhou Medical University, Taizhou, Zhejiang, China (Xu); Department of Neurology, Shanxi Provincial People's Hospital, Taiyuan, Shanxi, China (Y. Sun); Department of Neurology, Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou, Fujian, China (Yi); Department of Neurology, The First People's Hospital of Chenzhou, Chenzhou, Hunan, China (Feng); Department of Neurology, Linyi People's Hospital, Shandong, Linyi, China (Han); School of Biological Science and Medical Engineering, Beihang University, Beijing, Beijing, China (T. Liu); Department of Neurology, University of California at Los Angeles, Los Angeles, California (Liebeskind); Department of Neurology, Cooper Hospital University Medical Center, Camden, New Jersey (Jovin); Department of Neurology and Radiology, Boston Medical Center, Boston University Chobanian and Avedisian School of Medicine, Boston, Massachusetts (Nguyen); Department of Neurology, The University of Melbourne Medicine at Royal Melbourne Hospital, Melbourne, Victoria, Australia (Yan).

Author Contributions: Drs Huo and Yan 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 Miao, Luo, Song, D. Sun, Chen, and Yao contributed equally. Drs Yan and Huo contributed equally as co-senior authors.
Concept and design: Miao, D. Sun, Chen, Yao, Y. Liu, Wei, Cai, Xu, Y. Sun, Han, Mo, Deng, Xu Tong, B. Wang, T. Liu, Z. Li, Ren, Yilong Wang, Liebeskind, Nguyen, Yongjun Wang, L. Liu, Yan, Huo.
Acquisition, analysis, or interpretation of data: Miao, Luo, Song, D. Sun, Chen, Pan, Y. Liu, Yuan, Wen, Q. Yang, Z. Zhou, Chang, Nan, J. Wang, Xiang, L. Zhou, W. Gao, H. Zhang, Hao, Xu, Y. Sun, Yi, Feng, F. Gao, Ma, X. Sun, Deng, X. Li, Jia, B. Wang, He, M. Yang, Zhao, X. Zhang, L. Zhang, S. Li, Xin Tong, Jing, Xiong, Liebeskind, Jovin, Huo.
Drafting of the manuscript: Luo, D. Sun, Yao, Q. Yang, Nan, W. Gao, Xu, Y. Sun, Deng, B. Wang, X. Zhang, Yan, Huo.
Critical review of the manuscript for important intellectual content: Miao, Luo, Song, D. Sun, Chen, Pan, Y. Liu, Yuan, Wen, Wei, Cai, Z. Zhou, Chang, Nan, J. Wang, Xiang, L. Zhou, W. Gao, H. Zhang, Hao, Xu, Y. Sun, Yi, Feng, Han, F. Gao, Ma, Mo, X. Sun, Xu Tong, X. Li, Jia, B. Wang, He, M. Yang, Zhao, L. Zhang, S. Li, Xin Tong, Jing, Xiong, T. Liu, Z. Li, Ren, Yilong Wang, Liebeskind, Jovin, Nguyen, Yongjun Wang, L. Liu, Yan, Huo.
Statistical analysis: Miao, Chen, Yao, Pan, Nan, L. Zhou, Hao, Xu, Y. Sun, Feng, Deng, M. Yang, X. Zhang, Xin Tong, Huo.
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Supervision: Miao, Luo, Pan, Y. Liu, Yuan, Wen, Xu, Y. Sun, F. Gao, He, Zhao, Jing, T. Liu, Yilong Wang, Liebeskind, Jovin, Yongjun Wang, L. Liu, Yan, Huo.
Other: Chang, H. Zhang.

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