Title

Intra-arterial Tenecteplase Following Endovascular Reperfusion for Large-Vessel Occlusion Acute Ischemic Stroke: The POST-TNK Randomized Clinical Trial

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(3) Supplement 3 – eMethods, eFigures, and eTables

(4) Supplement 4 – Data sharing statement

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Key Points

Question

Does adjunctive intra-arterial tenecteplase following near-complete to complete reperfusion by endovascular thrombectomy improve freedom from disability in patients with large-vessel occlusion acute ischemic stroke?

Findings

In this randomized clinical trial that included 540 patients, treatment with intra-arterial tenecteplase resulted in freedom from disability (a modified Rankin Scale score of 0 or 1) in 49.1% vs 44.1% of patients at 90 days, respectively. This difference was not statistically significant (adjusted risk ratio, 1.15).

Meaning

Among patients with large-vessel occlusion stroke presenting within 24 hours of time last known well and who had achieved near-complete to complete reperfusion, adjunctive intra-arterial tenecteplase did not significantly increase the likelihood of freedom from disability.

ABSTRACT

IMPORTANCE The impact of adjunctive intra-arterial tenecteplase administration following near-complete to complete reperfusion by endovascular thrombectomy (EVT) for acute ischemic stroke is unknown.

OBJECTIVE To assess the efficacy and adverse events of adjunctive intra-arterial tenecteplase in patients with large-vessel occlusion (LVO) stroke and who had achieved near-complete to complete reperfusion (defined as the expanded Thrombolysis in Cerebral Infarction [eTICI] scale of 2c to 3) after EVT.

DESIGN, SETTING, AND PARTICIPANTS This investigator-initiated, randomized, open-labeled, blinded-outcome-assessment trial was implemented at 34 hospitals in China, enrolling 540 patients with stroke due to proximal intracranial LVO and with an eTICI of 2c to 3 without prior intravenous thrombolysis within 24 hours of time last known well. Recruitment took place between October 26, 2022, and March 1, 2024, with a final follow-up on June 3, 2024.

INTERVENTIONS Eligible patients were randomly assigned to intra-arterial tenecteplase (n = 269) at 0.0625mg/kg or no intra-arterial thrombolysis (n = 271).

MAIN OUTCOMES AND MEASURES The primary efficacy outcome was freedom from disability, defined as a score of 0 or 1 on the modified Rankin Scale (range, 0 [no symptoms] to 6 [death]) at 90 days. The primary safety outcomes were death at 90 days and symptomatic intracranial hemorrhage within 48 hours.

RESULTS Among 540 patients randomized (median age, 69 years; 221 female [40.9%]), 539 (99.8%) completed the trial. The proportion of participants with a modified Rankin Scale score of 0 or 1 at 90 days was 49.1% (132/269) in the intra-arterial tenecteplase group and 44.1% (119/270) in the control group (adjusted risk ratio, 1.15 [95% CI, 0.97-1.36]; *P* = .11). Ninety-day mortality was 16.0% and 19.3% (adjusted hazard ratio, 0.75 [95% CI, 0.50-1.13]; *P* = .16), respectively. The proportion of symptomatic intracranial hemorrhage was 6.3% and 4.4% (adjusted risk ratio, 1.43 [95% CI, 0.68-2.99]; *P* = .35), respectively.

CONCLUSIONS AND RELEVANCE In patients with acute ischemic stroke due to

LVO presenting within 24 hours of time last known well and who had achieved near-complete to complete reperfusion, adjunctive intra-arterial tenecteplase did not significantly increase the likelihood of freedom from disability at 90 days.

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Introduction

Endovascular thrombectomy (EVT) is the standard therapy for patients with acute ischemic stroke due to large-vessel occlusion (LVO).[1] While near-complete to complete reperfusion (eTICI 2c to 3) can be achieved in over 50% of patients with LVO, only approximately 40% of these patients are free of disability at 90 days post-stroke.[2,3] Infarct already existing at the time of procedure and infarct growth after the procedure into regions with insufficient macrocirculatory and microcirculatory reperfusion may lead to incomplete functional recovery.[4] Previous studies have shown that hypoperfusion was common in patients who underwent EVT despite successful reperfusion, which was associated with poor clinical outcomes.[5,6] The Chemical OptImization of Cerebral Embolectomy (CHOICE) trial investigators explored the use of adjunct intra-arterial alteplase versus placebo in patients with acute LVO stroke who had achieved successful reperfusion. The trial showed a benefit of adjunct intra-arterial alteplase in improving freedom from disability at 90 days without increasing the risk of symptomatic intracranial hemorrhage.[7] However, this trial was prematurely terminated due to lack of placebo supply.

Tenecteplase, compared with alteplase, is characterized by greater fibrin specificity, a longer half-life, and ease of administration as a single bolus.[8] The Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial showed that intravenous tenecteplase was associated with better reperfusion and functional outcome than intravenous alteplase in patients with LVO stroke.[9] A secondary analysis of the EXTEND-IA TNK showed that tenecteplase had higher early reperfusion compared to alteplase in patients who had low clot burden.[10]

The current study was designed to test the hypothesis that adjunctive intra-arterial tenecteplase, administered after near-complete to complete reperfusion during the EVT procedure, would provide a benefit to patients who had anterior circulation LVO and treated with EVT within 24 hours of last known well time.

Methods

Trial Design and Oversight

The Adjunctive Intra-arterial Tenecteplase Following Near-Complete to Complete Reperfusion for Large-Vessel Occlusion Stroke (POST-TNK) trial was a multicenter, prospective, randomized, open-label, blinded-outcome-assessment clinical trial and conducted at 34 comprehensive stroke centers in China. The trial protocol was approved by a central medical ethics committee and the research board of each participating center. All enrolled patients or their legally authorized representative provided written informed consent. A summary of the study protocol has been published[11] and the full protocol is available in Supplement 1. The statistical analysis plan is available in Supplement 2.

The trial was designed and conducted by a steering committee composed of independent academic investigators. The trial was monitored by an independent data and safety monitoring board. All data analyses and outcome adjudication were performed by an independent clinical events committee. The trial was conducted according to the Declaration of Helsinki Harmonization Guidelines. This study adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Participants

Patients were eligible for inclusion in the trial if they were 18 years or older; had a baseline National Institutes of Health Stroke Scale (NIHSS; range, 0 to 42, with higher scores indicating greater stroke severity) value of 25 or less; had acute ischemic stroke due to occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery (M1), or the second segment of the middle cerebral artery (M2); had an Alberta Stroke Program Early CT Score (ASPECTS; range, 0-10, with 1 point subtracted for early ischemic change in each defined region on the CT scan) of 6 or more if obtained within 6 hours of time last known well, or had an ASPECTS value of 7 or more or met the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3)[12] study criteria or the DWI or CTP Assessment with Clinical

Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN)[13] study criteria between 6 to 24 hours of last known well time, and had an eTICI score of 2c (90-99% macrocirculatory reperfusion) to 3 (100% macrocirculatory reperfusion) following EVT. Patients with prestroke disability (defined as a score of 2 to 6 on the modified Rankin Scale; the mRS score ranges from 0 [no symptoms] to 6 [death] for the evaluation of neurological functional disability), and treated with intravenous thrombolysis before the EVT were excluded. Detailed inclusion and exclusion criteria are provided in eMethod 1 in the Supplement 3.

Randomization and Masking

Eligible patients were randomly assigned in a 1:1 ratio to either the intra-arterial tenecteplase group or the control group using a permuted block randomization method with varying block sizes of 2, 4, or 6 through a web-based mobile phone app or computer. The study team members were blinded to the treatment randomization.

Intervention

Patients in both groups received EVT. In the intra-arterial tenecteplase group, patients underwent an infusion of intra-arterial tenecteplase with a dose of 0.0625 mg/kg (maximum dose 6.25 mg) for 10 to 15 minutes through a distal access catheter or microcatheter positioned proximal to the initially occluded artery. In the control group, the procedure was terminated without adjunctive intra-arterial thrombolysis.

Outcomes

The primary efficacy outcome was freedom from disability (mRS 0 or 1) at 90 days after randomization. The score assessment was based on central evaluation by video or audio by certified evaluators who were unaware of the treatment assignment. If video or audio recordings were unavailable, outcomes were determined in-person by certified

local investigators, who were also unaware of the treatment assignment. The mRS score assessors received additional training in the use of the mRS.[14,15]

The secondary efficacy outcomes included functional independence (mRS 0 to 2) at 90 days; level of disability (mRS shift analysis) at 90 days; the NIHSS change from baseline to 5 to 7 days or early to discharge if earlier; health-related quality of life measured with the European Quality of Life Five-Dimension Five-Level scale (EQ-5D-5L; range, -0.39 to 1, with lower scores indicating a worse quality of life) at 90 days.

The primary safety outcomes were death due to any cause within 90 days and symptomatic intracranial hemorrhage, according to the modified Heidelberg bleeding classification within 48 hours.[16] Other safety outcomes included any intracranial hemorrhage within 48 hours, systemic bleeding as defined according to the criteria established in the Global Utilization of Streptokinase and Tissue Plasminogen Activator of Occluded Coronary Arteries (GUSTO)[17] trial within 90 days, and adverse events (including serious adverse events).

Sample Size Calculation

We assumed the proportion of freedom from disability was 32.8% in the control group based on a previous study.[18] As an 18.6% absolute difference in the proportion of mRS 0-1 was reported in the CHOICE trial, we conservatively estimated a 13% difference between the two groups, which meant that the proportion of mRS 0-1 in the intra-arterial tenecteplase group would be 45.8%. A sample size of 236 patients per group would provide 83% power at a two-sided significance level of 0.05. Considering a 5% attrition rate, a total of 498 patients would be required (249 per group). When enrollment proceeded briskly and additional study agent was available, the sample size was increased to more than 498 to increase study power with the approval of the independent data and safety monitoring board.

Statistical Analysis

The primary analysis of the primary outcome was based on the complete case of the full analysis set, which included patients according to their randomization assignment, with a valid assessment of mRS at day 90 (eMethod 2 in the Supplement 3). The supportive per-protocol analyses for the primary and secondary outcomes included patients who received the complete intervention as specified in the protocol. Patients who received the randomized treatment but who had major protocol violations were not included in the per-protocol analysis. Analyses of adverse events were based on the safety population, which consisted of all randomized participants who received any study treatment.

The treatment effect for the primary outcome and binary outcomes was measured using a risk ratio (RR) by fitting the modified Poisson regression. Post hoc analyses were performed to calculate the risk difference (RD) using the generalized linear model. The treatment effect of the ordinal modified Rankin Scale score was estimated using the generalized odds ratio (GenOR).[19] Non-normal continuous secondary outcomes were analyzed using the win ratio (WR) approach.[20] The difference in mortality between two the treatment groups was measured by a hazard ratio (HR) using Cox regression model. The primary analyses for all outcomes were based on adjusted analyses for 5 prespecified covariates: age, baseline NIHSS score, baseline ASPECTS, occlusion site, and time from last known well to randomization, generating the point estimates of adjusted treatment effects with their 95% confidence intervals. The adjusted RR and HR were estimated by adding those covariates into modified Poisson regression and Cox regression models, respectively. The adjusted GenOR and WR[20] were estimated using the inverse probability of treatment weighting method. In addition, unadjusted treatment effects were calculated and reported.

Sensitivity analyses of the primary outcome were also performed including a per-protocol analysis; imputation of missing primary outcome under best-case, worst-case, and best-worst case scenarios, and using multiple imputations; and a generalized estimating equation model to control for possible center effect (eMethod 3 in the Supplement 3). Testing for modification of the treatment effect on the primary efficacy

and safety events was conducted in nine subgroups: age, sex, baseline NIHSS score, prestroke mRS, baseline ASPECTS score, time from last known well to randomization, stroke etiology, occlusion location, and eTICI grade. Interactions of intra-arterial tenecteplase treatment effect with each of the subgroup variables were explored by adding interactions of the subgroup variables with treatment to the modified Poisson regression.

For all outcomes, a 2-sided *P* value of less than 0.05 was considered to indicate statistical significance. All analyses of safety outcomes and secondary outcomes were considered exploratory and performed without adjustment for multiplicity. All statistical analyses were performed with the use of SAS software version 9.4 (SAS Institute) and R software version 4.3.0 (R Development Core Team; http://www.r-project.org).

Results

Characteristics of the Patients

From October 26, 2022 through March 1, 2024, a total of 541 patients were enrolled. One patient immediately withdrew consent after randomization, leaving 269 patients assigned to the intra-arterial tenecteplase group and 271 to the control group (**Figure 1**; eFigures 1 and 2 in Supplement 3). The demographic and clinical characteristics were well balanced in the two study groups (**Table 1**; eTable 1 in the Supplement 3). The median age of participants was 69 years (IQR, 59-76) in both groups, and 115 of 269 participants (42.8%) were female in the intra-arterial tenecteplase group and 106 of 271 participants (39.1%) were female in the control group. The median baseline NIHSS score was 15 (IQR, 11-20) in the intra-arterial tenecteplase group and 15 (IQR, 10-20) in the control group; the baseline median ASPECTS was 8 (IQR, 7-9) in both groups. The median time from last known well to randomization was 500 (IQR, 305-754) minutes in the intra-arterial tenecteplase group and 490 (IQR, 324-809) minutes in the control group.

352 **Primary Efficacy Outcome**

353 Freedom from disability occurred in 132 of 269 patients (49.1%) in the intra-arterial
354 tenecteplase group and in 119 of 270 patients (44.1%) in the control group at 90 days.
355 There was no significant difference in the proportion of 90-day freedom from disability
356 between the two groups, yielding an unadjusted RR of 1.11 (95% CI, 0.93-1.33) and an
357 adjusted RR of 1.15 (95% CI, 0.97-1.36; *P* = .11) (**Table 2** and **Figure 2**) as well as
358 unadjusted RD of 5.00% (95% CI, -3.42% to 13.41%). The per-protocol and the
359 sensitivity analyses yielded similar results (eTables 2, 3 and eFigure 3 in Supplement
360 3). Mode of assessment of the primary outcome was central rater analysis of recorded
361 video in 149 patients, central rater analysis of recorded audio in 299, local investigator
362 assessment in 10, known fatal outcome in 81.
363
364 **Secondary Efficacy Outcomes**

365 There were 165 of 269 patients (61.3%) who achieved an mRS score of 0 to 2 in the
366 intra-arterial tenecteplase group compared with 159 of 270 patients (58.9%) in the
367 control group (adjusted RR, 1.06 [95% CI, 0.93-1.21], *P* = .38). The median mRS score
368 at 90 days was 2 (IQR, 0-4) in the intra-arterial tenecteplase group and 2 (IQR, 0-4) in
369 the control group, a favorable shift in mRS distribution showing an unadjusted GenOR
370 of 1.17 (95% CI, 0.93-1.48) and an adjusted GenOR of 1.22 (95% CI, 0.96-1.55; *P*
371 = .10). There was no significant difference in other prespecified secondary efficacy
372 outcomes between the two groups (**Table 2**).
373
374 **Adverse Events**

375 Death occurred in 43 of 269 patients (16.0%) in the intra-arterial tenecteplase group
376 and in 52 of 270 patients (19.3%) in the control group, yielding an unadjusted HR of
377 0.81 (95% CI, 0.54-1.21) and an adjusted HR of 0.75 (95% CI, 0.50-1.13; *P* = .16).
378 Symptomatic intracranial hemorrhage occurred in 17 of 268 patients (6.3%) in the intra-
379 arterial tenecteplase group and in 12 of 271 patients (4.4%) in the control group
380 (unadjusted RR, 1.43 [95% CI, 0.70-2.91]; adjusted RR, 1.43 [95% CI, 0.68-2.99], *P*

= .35). Any radiologic intracranial hemorrhage occurred in 36.6% in the intra-arterial tenecteplase group and 27.3% in the control group (adjusted RR, 1.33; [95% CI, 1.04-1.69], $P = 0.02$). Other observed incidence of systemic bleeding events, adverse events, and serious adverse events did not differ substantially between the two groups (**Table 2**; eTables 4, 5 and eFigure 4 in Supplement 3).

Subgroup and Sensitivity Analyses

Subgroup analyses are shown in **Figure 3**. The results of subgroup analysis were generally consistent with the primary analysis, but no definite conclusions can be drawn from subgroup analysis.

Discussion

In patients with anterior circulation LVO presenting within 24 hours of last known well and who had achieved near-complete to complete reperfusion, the POST-TNK trial did not show a significant improvement in disability outcomes at 90 days with adjunctive intra-arterial tenecteplase. There was no significant difference in mortality or symptomatic intracranial hemorrhage between the two groups. The observed incidence of any radiographic intracranial hemorrhage was significantly higher in the intra-arterial tenecteplase group than in the control group.

This study differed from the CHOICE trial that examined the use of adjunct intra-arterial alteplase after successful angiographic reperfusion with thrombectomy.[7] First, CHOICE had a relatively small sample size. To our knowledge, the present study, including 540 participants, is the largest randomized trial that provides evidence on the effect of adjunctive intra-arterial tenecteplase in patients with LVO stroke within 24 hours of last known well and who had achieved near-complete to complete reperfusion by EVT. Second, nearly 60% of patients enrolled in the CHOICE trial were treated with intravenous thrombolysis before randomization. To mitigate hemorrhage risk with additional intra-arterial thrombolytic, patients who received intravenous thrombolysis before intervention were excluded in this trial. Third, CHOICE enrolled patients with

eTICI 2b (50-89%) reperfusion in addition to eTICI 2c to 3 while the POST-TNK trial only enrolled patients with eTICI 2c-3. However, the eTICI 2c to 3 subgroup showed statistically significant benefit in CHOICE.

The results for the primary outcome in this trial were neutral, but the confidence intervals do not exclude a clinically meaningful benefit of therapy. The treatment effect that the trial sample size was powered to detect of a 13% improvement in the rate of freedom from disability at 90 days was selected based on prior trial data and the realistic/pragmatic treatment difference approach.[21] However, the health state transition from mRS 0-1 to 2-6 is equally valued by patients as the transition from mRS 0-2 to 3-6[22] and for the latter outcome there is agreement among clinician-stakeholders that the minimal clinically important difference to change practice is 5% and real-world physician and patient behavior indicates the minimally clinically important difference for a simple, safe acute ischemic stroke treatment could be as low as 1.1% to 1.5%.[23-25] In parallel with this study, we conducted the Adjunctive Intra-arterial Urokinase after Near-complete to Complete Reperfusion for Acute Ischemic Stroke trail (POST-UK) to explore the efficacy and safety of intra-arterial urokinase adjunct to near-complete to complete reperfusion among patients with LVO stroke.[26] The POST-UK trial showed that intra-arterial urokinase did not significantly improve the rate of freedom from disability, although the width of the confidence intervals around the effect estimate in that trial also did not exclude a clinically meaningful benefit of intra-arterial thrombolysis.

For the safety outcomes, no significant difference in symptomatic intracranial hemorrhage was observed between the two groups in this trial. However, the overall rate of radiographic intracranial hemorrhage was significantly higher in the intra-arterial tenecteplase group compared to the control group. This overall response profile is similar to that of the Intra-arterial Tenecteplase after Endovascular Therapy in Acute Posterior Circulation Arterial Occlusion (ATTENTION IA) trial which also found non-significantly higher mRS 0-1 outcomes, non-significantly higher symptomatic hemorrhage, and significantly higher radiographic intracranial hemorrhage.[27]

Limitations

This trial has limitations. First, the trial was conducted in an open-label manner. Nevertheless, the outcomes were evaluated by clinicians who were unaware of the treatment assignments. Second, the trial excluded patients who received intravenous thrombolysis prior to EVT, so the results do not apply to these patients, limiting generalizability. Similarly, the trial was conducted in Asian patients and findings may not be generalizable to other populations who are known to have different stroke mechanism rates. Third, a follow-up angiogram and perfusion imaging were not required after the administration of tenecteplase. Therefore, improvement in reperfusion could not be measured in this study. The Safety and Efficacy of Intra-arterial Tenecteplase for Noncomplete Reperfusion of Intracranial Occlusions (TECNO, NCT05499832) and the CHOICE 2 (NCT05797792) trials will measure the effect of intra-arterial thrombolysis on improvement of reperfusion as an adjunct therapy to EVT. Fourth, multiple testing of secondary, safety outcome and subgroup analysis were not corrected for. Therefore, for these outcomes, differences and P values should be interpreted with caution.

Conclusions

Among patients with acute anterior-circulation LVO stroke who underwent EVT and achieved near-complete to complete reperfusion within 24 hours of last known well, adjunct intra-arterial tenecteplase did not show an improvement in freedom from disability. The mortality and symptomatic intracranial hemorrhage rates were similar in the two trial groups, though observed any intracranial hemorrhage was significantly higher with intra-arterial tenecteplase.

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Author Contributions:

Drs. Wenjie Zi and Yangmei Chen 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. Jiacheng Huang, Jie Yang, Chang Liu, Linyu Li, and Dahong Yang contributed equally as the co-first authors. *Concept and design:* Wenjie Zi, Jiacheng Huang, Yangmei Chen, Jie Yang, Chang Liu, Linyu Li, and Dahong Yang. *Acquisition, analysis, or interpretation of data:* All authors. *Drafting of the manuscript:* All authors. *Critical revision of the manuscript for important intellectual content:* Wenjie Zi, Jiacheng Huang, Jie Yang, Chang Liu, Linyu Li, Dahong Yang, Yangmei Chen, Thanh N. Nguyen, Johannes Kaesmacher, Raul G. Nogueira, and Jeffrey L. Saver. *Statistical analysis:* Duolao Wang, Changwei Guo. *Obtained funding:* Wenjie Zi, Yangmei Chen, and Chang Liu. *Administrative, technical, or material support:* All authors. *Supervision:* Wenjie Zi and Yangmei Chen.

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See Supplement 4.

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Figure Legends

Figure 1. Flow Chart of Patients Through the POST-TNK Trial.

[a] Baseline ASPECTS ≥6 based on non-contrast computed tomography (NCCT) within 6 hours of time last known well; ASPECTS ≥ 7 or meets the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) study criteria or meets the DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) study criteria between 6 to 24 hours of last known well time.

[b] One patient was lost to follow-up at 90 days.

[c] eFigure 1 in Supplement 3 provides detailed explanations of protocol violations.

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

Shown are the distribution of the scores on the modified Rankin scale among patients in the intra-arterial tenecteplase group and the control group. Scores range from 0 to 6, with 0 indicating no symptoms, 1, no clinically significant disability, 2, slight disability, 3, moderate disability, 4, moderately severe disability, 5, severe disability, and 6, death. Numbers indicate rounded proportions. One patient in the control group without valid assessment due to loss of follow-up was excluded from the chart. Treatment with intra-arterial tenecteplase was associated with an adjusted risk ratio of 1.15 (95% CI, 0.97-1.36; $P = .11$). The overall distribution of scores was not statistically significant in the ordinal logistic analysis (adjusted genOR, 1.22 [95% CI, 0.96-1.55]; $P = .10$).

Figure 3. Subgroup Analysis of the Primary Outcome.

NIHSS denotes National Institutes of Health Stroke Scale, mRS modified Rankin Scale, ASPECTS Alberta Stroke Program Early CT Score, eTICI expanded Thrombolysis in Cerebral Infarction, RR risk ratio. Forest plot of pre-specified subgroup analyses shows the risk ratio of primary efficacy outcome (defined as a score on the modified Rankin scale of 0 to 1) at 90 days. The age, baseline NIHSS, baseline ASPECTS, time from last known well to randomization were divided at median of the whole population as

prespecified in the statistical analysis plan. The widths of the confidence intervals were not adjusted for multiple comparisons, and the reported confidence intervals should not be used for hypothesis testing. One patient in the control group without valid assessment due to loss of follow-up was excluded from the chart. The sizes of the boxes in the plot correspond to the number of patients in each subgroup. The arrow indicates that the 95% CI was beyond the scale.

[a] Scores on the NIHSS range from 0 to 42, with higher scores indicating worse neurologic deficits.

[b] Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death). Five patients had modified Rankin scale 2 or more prior to enrollment and were not included in the test of interaction for subgroup analysis of pre-stroke mRS score. P for interaction here was not calculated because no treatment estimation was generated because of insufficient number of patients with pre-stroke mRS score of 1 or more.

[c] ASPECTS range from 0 to 10, with lower values indicating larger infarction.

[d] The TOAST classification system is a widely used method for classifying ischemic stroke and transient ischemic attack (TIA). It divides ischemic stroke and TIA into 5 subtypes based on their likely causes: large artery atherosclerosis, cardioembolism, small-artery occlusion, other determined etiology, and undetermined etiology.

[e] The eTICI scale is a reperfusion measure based on digital subtraction angiography, which ranges from 0 (no reperfusion) to 3 (complete reperfusion). One patient in the intra-arterial tenecetplase group and two patients in the control group had an eTICI grade less than 2c, and were not included in the test of interaction for subgroup analysis of eTICI scale.

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

Characteristics	No. (%)	
	Intra-arterial tenecteplase (n=269)	Control (n=271)
Age, median (IQR), y	69 (59-76)	69 (59-76)
Sex [a]		
Female	115 (42.8)	106 (39.1)
Male	154 (57.2)	165 (60.9)
Medical history [b]		
Hypertension	145 (53.9)	156 (57.6)
Atrial fibrillation	126 (46.8)	124 (45.8)
Stroke	55 (20.4)	44 (16.2)
Hyperlipidemia	50 (18.6)	57 (21.0)
Diabetes mellitus	45 (16.7)	56 (20.7)
Smoking [c]	83 (30.9)	78 (28.8)
Prestroke modified Rankin Scale score [d]		
0	255 (94.8)	260 (95.9)
1	11 (4.1)	9 (3.3)
Baseline NIHSS score, median (IQR) [e]	15 (11-20)	15 (10-20)
Baseline ASPECTS, median (IQR) [f]	8 (7-9)	8 (7-9)
Systolic blood pressure at hospital arrival median (IQR), mm Hg	141 (126-156)	147 (126-162)
Blood glucose level at hospital arrival median (IQR), mmol/L [g]	6.9 (6.2-8.3) [N = 250]	7.0 (5.9-8.3) [N = 261]
TOAST etiology [h]		
Cardioembolism	135 (50.2)	137 (50.6)
Large artery atherosclerosis	111 (41.3)	107 (39.5)
Other/Unknown	23 (8.6)	27 (10.0)
Occlusion site		
Internal carotid artery	57 (21.2)	59 (21.8)
M1 segment	172 (63.9)	166 (61.3)
M2 segment	40 (14.9)	46 (17.0)
Angiographic eTICI scores [i]		
2c	101 (37.5)	102 (37.6)
3	167 (62.1)	167 (61.6)
Time from last known well, median (IQR), min		
To start of EVT procedure	413 (249-694)	415 (251-740)
To randomization	500 (305-754)	490 (324-809)
To study treatment [j]	504 (310-760)	-

Abbreviation: ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale; eTICI, the expanded Thrombolysis in Cerebral Infarction; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

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

[a] Sex reported by the patient and verified by identification card.

[b] Comorbidities based on family or patient report.

[c] Current or within the prior 5 years.

[d] Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death). Three patients in the Intra-arterial tenecteplase group and two patients in the Control group had a prestroke score on the modified Rankin Scale of 2 or more.

[e] Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurological deficits.

[f] The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is an imaging measure of the extent of ischemic stroke. Scores range from 0 to 10, with higher scores indicating a smaller infarct core. Listed are values for the core laboratory assessment.

[g] Data on glucose at baseline were missing for 19 patients in the intra-arterial tenecteplase group and 10 patients in the control group.

[h] The TOAST classification system is a widely used method for classifying ischemic stroke and transient ischemic attack (TIA). It divides ischemic stroke and TIA into 5 subtypes based on their likely causes: large artery atherosclerosis, cardioembolism, small-artery occlusion, other determined etiology, and undetermined etiology.

[i] The expanded Thrombolysis in Cerebral Infarction (eTICI) scale is a reperfusion measure based on digital subtraction angiography, which ranges from 0 (no reperfusion) to 3 (complete reperfusion). One patient in the intra-arterial tenecetplase group and two patients in the control group had an eTICI grade less than 2c.

[j] Study treatment refers to the application of intra-arterial tenecteplase therapy.

676 **Table 2. Study outcomes.**

Outcome	No./total (%) Intra-arterial tenecteplase (N=269)	Control (N=270)	Unadjusted Risk Difference (95% CI)	Unadjusted Value (95% CI)	Adjusted Value (95% CI) [a]	*P* value
Primary outcome						
mRS score of 0 to 1 at 90 days [b]	132 (49.1)	119 (44.1)	5.00% (-3.42% to 13.41%)	RR: 1.11 (0.93 to 1.33)	RR: 1.15 (0.97 to 1.36)	0.11
Secondary outcomes						
mRS score of 0 to 2 at 90 days	165 (61.3)	159 (58.9)	2.45% (-5.82% to 10.71%)	RR: 1.04 (0.91 to 1.20)	RR: 1.06 (0.93 to 1.21)	0.38
mRS score at 90 days, no. of wins/total no. of pairs (%) [c]	32174/72630 (44.3)	27411/72630 (37.7)		GenOR: 1.17 (0.93 to 1.48)	GenOR: 1.22 (0.96 to 1.55)	0.10
mRS score at 90 days, median (IQR)	2 (0 to 4)	2 (0 to 4)				
Change in NIHSS score at 5-7 days or discharge if earlier, from baseline, no. of wins/total no. of pairs (%) [d,e]	38768/72899 (53.2)	31451/72899 (43.1)		WR: 1.23 (1.01 to 1.51)	WR: 1.19 (0.97 to 1.46)	0.10
Change of NIHSS score at 5-7 days or discharge if earlier, from baseline, median (IQR) [d]	-7 (-12 to -2)	-6 (-10 to -2)				
EQ-5D-5L score at 90 days, no. of wins/total no. of pairs (%) [f]	31640/72630 (43.6)	27360/72630 (37.7)		WR: 1.16 (0.92 to 1.46)	WR: 1.20 (0.95 to 1.52)	0.13
EQ-5D-5L score at 90 days, median (IQR)	0.9 (-0.1 to 1.0)	0.8 (-0.2 to 1.0)				
Primary safety outcomes						

Death within 90 days	43 (16.0)	52 (19.3)		HR: 0.81 (0.54 to 1.21)	HR: 0.75 (0.50 to 1.13)	0.16
Symptomatic intracranial hemorrhage within 48h [d, g]	17/268 (6.3)	12/271 (4.4)	1.92% (-1.90% to 5.73%)	RR: 1.43 (0.70 to 2.91)	RR: 1.43 (0.68 to 2.99)	0.35
Secondary safety outcomes						
Any radiologic intracranial hemorrhage within 48h [d, h]	98/268 (36.6)	74/271 (27.3)	9.26% (1.43% to 17.10%)	RR: 1.34 (1.04 to 1.72)	RR: 1.33 (1.04 to 1.69)	0.02
Systemic Bleeding [d, i]						0.11 [j]
Mild	27 (10.0)	32 (11.8)				
Moderate	0 (0.0)	2 (0.7)				
Severe	104 (38.7)	82 (30.3)				

Abbreviations: mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; EQ-5D-5L, European Quality of Life Five-Dimension Five-Level scale. RR, risk ratio; RD, risk difference; GenOR, generalized odds ratio; WR, win ratio.

[a] Adjusted values were adjusted for age, baseline NIHSS score, baseline ASPECTS score, occlusion site, and time from last known well to randomization. The GenOR and win ratio were adjusted using the inverse probability treatment weighting method. Post hoc analyses were performed to calculate the risk difference using the generalized linear model.

[b] The modified Rankin Scale of functional disability ranges from 0 (no symptoms) to 6 (death). Data was missing for 1 patient in the control group.

[c] The Win proportion was calculated by the number of wins in the intra-arterial tenecteplase group over the control group in mRS among all possible pairs of mRS taking one patient from the intra-arterial tenecteplase group and one patient from the control group divided by the total number of pairs. The results were adjusted using the inverse probability treatment weighting method. Data for modified Rankin Scale score was missing for 1 patient in the control group. The GenOR indicated the probability of modified Rankin Scale score was lower than the other group.

[d] All outcomes assessed within the first 7 days are analyzed in 271 patients in the intra-arterial tenecteplase group and 269 patients in the control group, including the 1 patient in the control group who was lost to follow-up between 1 week and 90 days

[e] Scores on the NIHSS range from 0 to 42, with higher values reflecting more severe neurologic impairment.

[f] EQ-5D-5L is a continuous scale measure of self-reported quality of life. Scores range from -0.39 to 1, with lower scores indicating a worse quality of life. Data was missing for 1 patient in the control group.

[g] Symptomatic intracranial hemorrhage was defined according to the modified 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). Data were not available for 1 patient in the intra-arterial tenecteplase group.

[h] Data were not available for 1 patient in the intra-arterial tenecteplase group.

[i] Bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria as follows: severe bleeding was defined as fatal or intracranial hemorrhage or other hemorrhage causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention; moderate bleeding as bleeding that required transfusion of blood

but did not lead to hemodynamic compromise requiring intervention; and mild bleeding as bleeding not requiring transfusion and not causing hemodynamic compromise (e.g., subcutaneous bleeding, mild hematomas, and oozing from puncture sites).

[j] Chi-square Test

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