## Title

Intra-arterial Urokinase after Endovascular Reperfusion for Acute Ischemic Stroke: The POST-UK Randomized Clinical Trial

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**(1)** Supplement 1 – Trial Protocol

**(2)** Supplement 2 – Statistical Analysis Plan

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

**(4)** Supplement 4 – Data sharing statement

**(5)** Supplement 5 – CONSORT Checklist

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**Key Points:**

**Question** Among patients with acute ischemic stroke caused by large vessel occlusion within 24 hours, does intra-arterial thrombolysis by urokinase administered after near-complete to complete reperfusion by thrombectomy improve clinical outcomes?

**Findings** In this randomized clinical trial that included 534 patients, proportion of survival without disability measured by the modified Rankin scale score of 0 or 1 at 90 days was 45.1% in the intra-arterial urokinase group, and 40.2% in the control group, with an adjusted risk ratio of 1.13.

**Meaning** Adjunctive intra-arterial urokinase to endovascular thrombectomy for acute ischemic stroke did not significantly improve the proportion of survival without disability.

**ABSTRACT**

**IMPORTANCE** Persisting or new thrombi in the distal arteries and the microcirculation have been reported to limit the benefits of successful thrombectomy for acute ischemic stroke patients. It remains uncertain whether intra-arterial thrombolysis by urokinase following near-complete to complete reperfusion by thrombectomy improves outcomes among patients with ischemic stroke due to large-vessel occlusion (LVO).

**OBJECTIVE** To assess the efficacy and adverse events of intra-arterial urokinase after near-complete to complete reperfusion by thrombectomy for acute ischemic stroke patients with LVO.

**DESIGN, SETTING, AND PARTICIPANTS** This investigator-initiated, randomized, open-label, blinded-endpoint trial was implemented at 35 hospitals in China, enrolling 534 patients with proximal intracranial LVO presenting within 24 hours of time last known well without intravenous thrombolysis after achieving near-complete or complete reperfusion by endovascular thrombectomy. Recruitment took place between November 15, 2022, and March 29, 2024, with final follow-up on July 4, 2024.

**INTERVENTIONS** Eligible patients were randomly assigned to intra-arterial urokinase group (a single dose of intra-arterial 100,000 IU urokinase injected in the initial target territory, n=267) or control group (without intra-arterial thrombolysis, n=267).

**MAIN OUTCOMES AND MEASURES** The primary efficacy outcome was the proportion of patients achieving survival without disability (modified Rankin scale score of 0 or 1) at 90 days. The primary safety outcomes were mortality at 90 days and incidence of symptomatic intracranial hemorrhage within 48 hours.

**RESULTS** A total of 534 patients were enrolled (median age, 69; 223(41.8%) female), and 532(99.6%) completed the trial. The percentage of patients with survival without disability at 90 days was 45.1% (120/266) in the intra-arterial urokinase group and 40.2% (107/266) in control group (adjusted risk ratio, 1.13 [95%CI, 0.94-1.36], $P$ = .19). The mortality (18.4% vs. 17.3%, adjusted hazard ratio 1.06 [95%CI, 0.71-1.59], $P$ = .77)

and incidence of symptomatic intracranial hemorrhage (4.1% vs. 4.1%, adjusted risk ratio 1.05 [95%CI 0.45-2.44], $P = .91$) were not significantly different between groups.

**CONCLUSIONS AND RELEVANCE** Among patients with acute ischemic stroke due to LVO, adjunct intra-arterial urokinase after near-complete to complete reperfusion by thrombectomy did not significantly increase the likelihood of survival without disability at 90 days.

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## Introduction

In the endovascular era, effectively restoring blood flow for occluded large vessels with endovascular thrombectomy has profoundly transformed the treatment algorithm for affected patients with acute ischemic stroke.[1] However, despite near-complete to complete reperfusion (expanded Thrombolysis In Cerebral Infarction [eTICI] scale 2c-3, indicating 90-100% reperfusion of visible vessels) with thrombectomy, less than half of stroke patients are disability-free at 90 days.[2] Angiographic recanalization of a proximal intracranial large vessel by thrombectomy may not translate to effective reperfusion of the microvascular circulation.[3] Persisting or new visible thrombi in distal arteries and nonvisible thrombi in the microcirculation can impair perfusion of the cerebral tissue, promote infarct growth after intervention, and reduce the likelihood of neurological recovery[4,5]. Targeting these thrombi, the Chemical Optimization of Cerebral Embolectomy (CHOICE) phase IIb trial suggested that intra-arterial infusion of a thrombolytic agent after successful endovascular thrombectomy may be a promising adjuvant strategy to improve the chances of a patient to achieve survival without disability. However, the CHOICE trial terminated prematurely with a limited sample size, which may result in increased variance in the estimation of the treatment effect.

Urokinase is an affordable and accessible thrombolytic drug that is widely used in low- and middle-income countries.[6] Intra-arterial urokinase was applied as a reasonable adjunct to unsuccessful thrombectomy in previous trials and current Chinese guidelines [7-9] Recently, a number of pilot or retrospective studies evaluated intra-arterial urokinase as an adjunctive treatment in large vessel occlusion stroke but had conflicting results.[10-12] The efficacy and safety of intra-arterial urokinase in acute ischemic stroke after successful endovascular thrombectomy remains unknown.

We initiated the Adjunctive Intra-arterial Urokinase after Near-complete to Complete Reperfusion for Acute Ischemic Stroke (POST-UK) trial to investigate the efficacy and safety of intra-arterial low-dose urokinase among patients with acute ischemic stroke due to large-vessel occlusion stroke following near-complete to

complete reperfusion by endovascular thrombectomy within 24 hours of last known well time.

## Methods

### *Trial Design and Oversight*

The trial of Adjunctive Intra-arterial Urokinase after Near-complete to Complete Reperfusion for Acute Ischemic Stroke (POST-UK) was an investigator-initiated, multicenter, prospective, randomized, open-label, blinded end-point (PROBE) trial, conducted in 35 comprehensive stroke centers across China. Trial centers, investigators, and committee members are listed in the Supplement 3. This trial had the approval by the Human Research Ethics Committee of the coordinating medical center, and the ethics board at each site before enrollment. Signed informed consent was obtained from the patient or their legally authorized representative before randomization. A condensed study protocol has been published[13] and the full text 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 (DSMB). All data analyses and outcomes adjudications 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*

Eligible patients were aged 18 years or older, diagnosed with an occlusion of the intracranial segment of the internal carotid artery, the first segment of the middle cerebral artery (M1), or the second segment of the middle cerebral artery (M2), with baseline National Institutes of Health Stroke Scale (NIHSS, range, 0 to 42, with higher scores indicating greater stroke severity) 25 or less, who had been able to complete usual activities in daily life without support before the stroke (modified Rankin Scale

[mRS] score <2; the mRS score ranges from 0 [no symptoms] to 6 [death] for the evaluation of neurologic functional disability), without prior intravenous thrombolysis, and were enrolled up to 24 hours from symptom onset, defined as time last known well. Patients were eligible if they had a small to moderate ischemic core (Baseline Alberta Stroke Program Early CT Score (ASPECTS) ≥ 6 based on non-contrast computed tomography (NCCT) if obtained within 6 hours; or ASPECTS ≥ 7 or met the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3)[14] 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)[15] study criteria between 6-24 hours) and had achieved an eTICI grade ≥ 2c by endovascular thrombectomy. Detailed inclusion and exclusion criteria are provided in eMethod 1 in Supplement 3.

***Randomization***

Eligible patients were randomly assigned in a 1:1 ratio to the intra-arterial urokinase group or the control group. Randomization was performed via a web-based mobile phone app or computer using a permuted block randomization method with randomly selected block sizes of 2, 4, or 6. The assessment of the trial outcomes was performed by qualified physicians, who were blinded to the treatment assignments.

***Interventions***

Endovascular treatment was carried out according to the usual practice of each center. Patients in the intra-arterial urokinase group received a single dose of intra-arterial urokinase (100,000 IU), which was reconstituted with 10 ml of 0.9% sterile normal saline for 10 to 15 minutes through a distal access catheter or microcatheter positioned proximal to the initially occluded artery. Patients in the control group terminated their procedures without intra-arterial adjunctive thrombolysis therapy. Medical centers participating in this research were expected to adhere to stroke national practice guidelines for concomitant medical therapy.[16]

### *Outcome Measures*

The primary efficacy outcome was survival without disability (score of 0 or 1 on mRS) at 90 days after randomization.[17] The score assessment was based on central evaluation by video or audio by certified evaluators who were unaware of the treatment assignment. The mRS score assessors received additional training and were authorized in the adjudication of the mRS.[18,19] If video or audio recordings were unavailable, outcomes were determined in-person by local investigators, who were also unaware of the treatment assignment. The secondary efficacy outcomes included functional independence (mRS score 0 to 2) at 90 days, the level of disability (shift analysis of mRS score) at 90 days, the change of the NIHSS score from baseline to 5-7 days or discharge if earlier, and health-related quality of life measured with the European Quality of Life 5-Dimension 5-Level questionnaire (EQ-5D-5L; range, -0.39 to 1 with higher scores denoting better quality of life) at 90 days.

The primary safety outcomes were death from any cause within 90 days and symptomatic intracranial hemorrhage defined by the modified Heidelberg Bleeding Classification within 48 hours of thrombectomy.[20] Other prespecified safety measures included any intracranial hemorrhage within 48 hours, and systemic bleeding event evaluated by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria (GUSTO) within 90 days.[21] Other adverse events and serious adverse events were also recorded.

### *Sample Size Calculation*

Based on our preceding Endovascular Treatment With vs Without Tirofiban for Patients with Large Vessel Occlusion Stroke (RESCUE BT) trial, we assumed that the proportion of patients with survival without disability (mRS 0-1) would be 32.8% in the control group with an eTICI of 2c-3[22]. Compared to an 18.6% absolute difference of the mRS 0-1 in the CHOICE trial, we assumed conservatively a 13% difference between the control group and the treatment group, where the proportion of mRS 0-1

in the treatment group would be 45.8%[22,23]. To demonstrate a 13% absolute difference with a type-1 error alpha of 0.05 (two-tailed) with a power of 83%, a sample size of 472 patients would be needed (236 patients per group). Taking into account a 5% attrition rate, a total of 498 patients (249 per group) was required. 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 DSMB.

***Statistical Analysis***

The primary outcome was based on a complete case analysis of the primary analysis set, which included patients according to their randomization assignment, with a valid assessment of mRS at day 90 (eMethod 2 in Supplement 3). The primary efficacy outcome of mRS 0-1 and other dichotomized outcomes were analyzed by fitting the modified Poisson regression models, and compared using a risk ratio (RR). The post-hoc risk difference (RD) was also calculated from analysis of the dichotomized outcomes using a generalized linear model. The score on the modified Rankin scale was compared using the generalized odds ratio (GenOR).[24,25] The change of NIHSS score from baseline to 5-7 days or at early discharge, and EQ-5D-5L at 90 days were compared using the win ratios.[25] The time to event outcome of 90-day mortality was compared using a hazard ratio from a Cox regression model. Both unadjusted and adjusted treatment effects were estimated in terms of point estimates and their 95% confidence intervals (CI). The adjusted analyses of binary outcomes and mortality were performed by adjusting for the following prespecified covariates in the modified Poisson models and Cox models, respectively: age, baseline NIHSS scores, baseline ASPECTS, occlusion site, and time from last known well to randomization. For the adjusted GenOR and win ratio analyses, the inverse-probability of treatment weighting method was employed. Both the crude and adjusted treatment effects and their 95% CIs were reported.[25]

We also performed sensitivity analyses of the primary analysis, including per-protocol analysis, imputation of missing primary outcome under different scenarios,

multiple imputation, and a generalized estimating equation model to control for possible center effect (eMethod 3 in Supplement 3). Patients who had received the randomized treatment but with 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. 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, time from last known well to randomization, stroke etiology, occlusion location, and eTICI grade. Interactions of 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*

Between November 15, 2022, and March 29, 2024, a total of 535 patients were enrolled. One patient immediately withdrew consent after randomization, leaving 267 patients assigned to the intra-arterial urokinase group and 267 to the control group (**Figure 1**, eFigures 1-2 in Supplement 3). There was no patient crossover to the other treatment group. Two patients (one in each assignment group) were lost to follow-up at 90 days.

The demographic and clinical characteristics of the patients at baseline were similar in the two trial groups (**Table 1**, and eTable 1 in Supplement 3). The median baseline NIHSS score was 15 (IQR, 11 to 19) in the intra-arterial urokinase group and 15 (IQR, 10 to 19) in the control group, respectively. The median ASPECTS was 8 (IQR, 7 to 9) in both groups. The median last known well time to randomization was

523 minutes (IQR, 312 to 779) in the intra-arterial urokinase group and 524 minutes (IQR, 318 to 817) in the control group.

***Primary Efficacy Outcome***

In the primary analysis, survival without disability (score of 0 or 1 on the modified Rankin scale) occurred in 120 of 266 patients (45.1%) in the intra-arterial urokinase group and 107 of 266 patients (40.2%) in the control group, yielding an unadjusted RD of 4.89% (95% CI, -3.51% to 13.28%) and an adjusted RR of 1.13 (95% CI, 0.94-1.36; $P$ = .19) (**Table 2** and **Figure 2**). The per-protocol analyses yielded similar results (eTable 2 and eFigure 3 in Supplement 3). Mode of assessment of the primary outcome was central rater analysis of recorded video in 58 patients, central rater analysis of recorded audio in 409, local investigator assessment in 7, known fatal outcome in 58.

***Secondary Efficacy Outcomes***

Functional independence (mRS score of 0 to 2) at 90 days occurred in 143 of 266 patients (53.8%) in the intra-arterial urokinase group and 139 of 266 (52.3%) patients in the control group (adjusted RR 1.04 [95% CI, 0.89-1.20]; $P$ = .64). The median 90-day mRS score was 2 (IQR, 0-5) in the intra-arterial urokinase group vs 2 (IQR, 1-4) in the control group, a favorable shift in mRS distribution showing an adjusted GenOR 1.07 (95%CI, 0.84 to 1.35; $P$ = .59). There were no significant differences of other prespecified secondary efficacy outcomes between the two groups (**Table 2**).

***Adverse Events***

Death occurred in 49 of 266 patients (18.4%) in the intra-arterial urokinase group and 46 of 266 patients (17.3%) in the control group (adjusted hazard ratio, 1.06 [95% CI, 0.71-1.59]; $P$ = .77). Symptomatic intracranial hemorrhage occurred in 11 (4.1%) patients in the intra-arterial urokinase group and 11 patients (4.1%) in the control group (adjusted RR, 1.05 [95% CI, 0.45-2.44]; $P$ = .91). The incidence of any radiologic intracranial hemorrhage was 69 (25.8%) in the intra-arterial urokinase group and 66

patients (24.7%) in the control group (adjusted RR, 1.10 [95% CI, 0.82-1.47]; *P* = .52). The observed incidence of systemic bleeding, adverse events and serious adverse events did not differ between the groups (**Table 2**; eTables 4-5 and eFigure 4 in Supplement 3).

### *Subgroup and Sensitivity Analyses of Primary Outcome*

The results of subgroup analyses are exhibited in **Figure 3**. The sensitivity analyses were consistent to the primary analysis, but no definite conclusions can be drawn from sensitivity analyses and subgroup analysis (eTable 3 in Supplement 3).

## Discussion

In this multicenter randomized clinical trial, intra-arterial urokinase administered after near-complete to complete reperfusion by thrombectomy did not significantly improve the likelihood of survival without disabilitys among patients with acute ischemic stroke caused by anterior circulation large vessel occlusion. The incidence of symptomatic intracranial hemorrhage, mortality, any intracranial hemorrhage, and systemic bleeding did not differ significantly between two groups.

There are several potential explanations for non-positive results with respect to intra-arterial urokinase. First, the baseline characteristics of enrolled patients in this trial differed from those enrolled in the CHOICE trial, including the lower proportion of M2 occlusion, higher baseline NIHSS, lower ASPECTS, and higher proportion of intracranial atherosclerosis, which might have led to the different outcomes in this trial.[26-28] Although the sample size of this trial was over four times as large as the sample size in the CHOICE trial, we still failed to show the benefit of adjunct intra-arterial urokinase. Second, the prevalence of microcirculatory impairment in cerebral tissues has been reported to be approximately 30% after successful angiographic reperfusion.[3] This study administered intra-arterial urokinase to all eligible patients, which might have diluted a potential treatment effect by the inclusion of patients who have complete tissue reperfusion. Performing a perfusion study after successful angiographic

reperfusion might have informed enrollment.[29] However flat panel perfusion imaging is not available in most angiography suites and transporting patients to CT perfusion with a sheath in place would have been logistically challenging.[30] Even so, safety or adverse events were not worse in the urokinase group. Third, there may be no genuine benefit of urokinase for this indication.

Although the primary efficacy outcome in this trial did not show a statistically significant result, the confidence intervals do not exclude a clinically meaningful benefit of therapy. The treatment effect that the trial sample size was powered to detect was selected based on applying a realistic/pragmatic treatment difference approach to prior trial data.[31] However, for the similarly valued health state transition for mRS 0-2 to 3-6 as the analyzed transition from mRS 0-1 to 2-6 the minimal clinically important difference to change practice per clinician stakeholders and the minimal clinically important difference of value to patients are lower than the effect size that we used to power this trial.[32-35] In addition, non-survival without disability (mRS 2-6) rates were substantially lower in the control group of the current trial than the control groups of the pivotal endovascular thrombectomy trials, about 59% vs 73%, probably due to inclusion of only patients with near complete to complete reperfusion in this study.[36] As a result, fewer control patients in the current study provided an opportunity to contribute to treatment effect detection of patients achieved survival without disability. Studies seeking to advance endovascular thrombectomy care are now subject to the challenge of diminishing control failure rates to trial conduct.[37,38]

For the safety outcomes, no significant difference in symptomatic intracranial hemorrhage or radiographic intracranial hemorrhage was observed between the two groups in this trial. As the neutral results but the significantly higher rates of radiographic intracranial hemorrhage in the Intra-arterial Tenecteplase after Endovascular Therapy in Acute Posterior Circulation Arterial Occlusion (ATTENTION IA) trial and the Adjunctive Intra-arterial Tenecteplase Following Near-Complete to Complete Reperfusion for Large-Vessel Occlusion Stroke (POST-TNK) trials compared to their control groups, urokinase did not significantly increase the rate of

intracranial hemorrhage and safety events.[39,40]

**Limitations**

This trial has several limitations. First, the trial was open-label, though outcomes were assessed by clinicians who were unaware of the treatment assignments. Second, 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. Third, we did not require cerebral angiography after study drug treatment due to the difficulties in identifying microcirculation disturbance from a normal cerebral angiogram after mechanical thrombectomy. Forth, to mitigate hemorrhage risk with additional intra-arterial thrombolysis, patients who received intravenous thrombolysis before intervention were excluded in this trial, which might alter the outcomes in both groups. Fifth, since the trial was conducted in China, where intracranial atherosclerosis is more prevalent, the generalizability of the trial results will require further exploration in other populations.

**Conclusion**

Among patients with large vessel occlusion acute ischemic stroke achieving near-complete to complete reperfusion, adjunctive intra-arterial urokinase after endovascular thrombectomy did not result in a significant difference in the proportion of survival without disability at 90 days.

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**Author Contributions:**

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

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**Data Sharing Statement:**

See Supplement 4.

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40. The citation for POST-TNK

## Figure legends:

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

[a] Baseline Alberta Stroke Program Early CT Score (ASPECTS) ≥6 based on non-contrast computed tomography (NCCT) if the onset time is within 6 hours; 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.

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

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

Shown are the scores on the modified Rankin scale of all included patients with available 90-day follow-up data. The primary analysis set included all the patients who provided consent, and patients were included in the analysis according to their assigned trial group. Scores range from 0 to 6, with 0 indicating no symptoms or disability after stroke, 1 no clinically relevant disability, 2 slight disability, 3 moderate disability, 4 moderate-to-severe disability, 5 severe disability (complete dependence on daily care), and 6 death. Percentages not total 100 because of rounding. Treatment with intra-arterial urokinase was associated with an adjusted risk ratio of 1.13 (95% CI, 0.94-1.36; $P$ = .19) for survival without disability. Data was missing for 1 patient in the intra-arterial urokinase group and 1 patient in the control group.

**Figure 3. Subgroup analyses.**

Forest plot showed the pre-specified subgroup analyses for the risk ratio of survival without disability (defined as a score on the modified Rankin scale of 0 to 1) at 90 days. The widths of the confidence intervals were not adjusted for multiple comparisons, and the reported confidence intervals should not be used for hypothesis testing. Numbers are patients per group. NIHSS denotes National Institutes of Health Stroke Scale, mRS modified Rankin Scale score, ASPECTS Alberta Stroke Program Early Computed

Tomography Score, LKW last known well, ICA internal carotid artery terminus, M1 and M2 the first and second middle cerebral artery segments, eTICI expanded Thrombolysis In Cerebral Infarction. 1 patient in the control group and 1 patient in the intra-arterial urokinase group without valid assessment due to loss of follow-up were not included in the chart. 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 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). Four patients had a modified Rankin Scale score higher than 1 prior to enrollment, including one patient who was lost to follow-up, who were not shown in the chart.

[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] Five patients with an eTICI grade lower than 2c, including one patient who was lost to follow-up, were not shown in the chart.

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

| Characteristics | No. (%) Intra-arterial urokinase (N=267) | Control (N=267) |
|---|---|---|
| Age, median (IQR), y | 69 (59–77) | 68 (58–76) |
| Sex [a] | | |
| Female | 105 (39.3) | 118 (44.2) |
| Male | 162 (60.7) | 149 (55.8) |
| Medical history [b] | | |
| Hypertension | 169 (63.3) | 163 (61.0) |
| Atrial fibrillation | 97 (36.3) | 102 (38.2) |
| Hyperlipidemia | 58 (21.7) | 66 (24.7) |
| Stroke | 57 (21.3) | 52 (19.5) |
| Diabetes mellitus | 55 (20.6) | 62 (23.2) |
| Smoking [c] | 68 (25.5) | 56 (21.0) |
| Prestroke modified Rankin Scale score [d] | | |
| 0 | 256 (95.9) | 254 (95.1) |
| 1 | 9 (3.4) | 11 (4.1) |
| Baseline NIHSS score, median (IQR) [e] | 15 (11–19) | 15 (10–19) |
| Baseline ASPECTS, median (IQR) [f] | 8 (7–9) | 8 (7–9) |
| Systolic blood pressure at hospital arrival median (IQR), mm Hg | 144 (131–168) | 143 (128–160) |
| Blood glucose level at hospital arrival median (IQR), mmol/L [g] | 7.1 (6.1–8.7) [N = 239] | 6.9 (6.1–8.6) [N = 229] |
| TOAST etiology [h] | | |
| Cardioembolism | 103 (38.6) | 106 (39.7) |
| Large artery atherosclerosis | 136 (50.9) | 131 (49.1) |
| Other/Unknown | 28 (10.4) | 30(11.3) |
| Occlusion site | | |
| Internal carotid artery | 57 (21.3) | 68 (25.5) |
| M1 segment | 161 (60.3) | 148 (55.4) |
| M2 segment | 49 (18.4) | 51 (19.1) |
| Angiographic eTICI scores [i] | | |
| 2c | 96 (36.0) | 90 (33.7) |
| 3 | 168 (62.9) | 175 (65.5) |
| Time from last known well, median (IQR), min | | |
| To start of EVT procedure | 462 (260–730) | 465 (255–753) |
| To randomization | 523 (312–779) | 524 (318–817) |
| To study treatment [j] | 529 (322–787) | — |

Abbreviation: ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; eTICI, The expanded Thrombolysis In Cerebral Infarction; 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 modified Rankin Scale score of functional disability range from 0 (no symptoms) to 6 (death). Two patients in the Intra-arterial urokinase 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 28 patients in the intra-arterial urokinase group and 38 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). 3 patients in the Intra-arterial urokinase group and 2 patients in the Control group had an eTICI grade of less than 2c.

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

**Table 2. Study Outcomes.**

| Outcome | No./total (%) | | Unadjusted Risk Difference (95% CI) | Unadjusted Value (95% CI) | Adjusted Value (95% CI) [a] | P value |
|---|---|---|---|---|---|---|
| | Intra-arterial urokinase (N=266) | Control (N=266) | | | | |
| **Primary outcome** | | | | | | |
| mRS score of 0 to 1 at 90 days [b] | 120 (45.1) | 107 (40.2) | 4.89% (-3.51% to 13.28%) | RR: 1.12 (0.92 to 1.37) | RR: 1.13 (0.94 to 1.36) | 0.19 |
| **Secondary outcomes** | | | | | | |
| mRS score of 0 to 2 at 90 days | 143 (53.8) | 139 (52.3) | 1.50% (-6.98% to 9.99%) | RR: 1.03 (0.88 to 1.21) | RR: 1.04 (0.89 to 1.20) | 0.64 |
| mRS score at 90 days, no. of wins/total no. of pairs (%) [c] | 30466/70756 (43.1) | 28619/70756 (40.5) | | GenOR: 1.06 (0.84 to 1.34) | GenOR:1.07 (0.84 to 1.35) | 0.59 |
| mRS score at 90 days, median (IQR) | 2 (0 - 5) | 2 (1 - 4) | | | | |
| Change in NIHSS score at 5-7 days or discharge if earlier, from baseline, no. of wins/total no. of pairs (%) [d, e] | 37252/71289 (52.3) | 31138/71289 (43.7) | | WR: 1.20 (0.97 to 1.47) | WR: 1.17 (0.95 to 1.45) | 0.13 |
| Change of NIHSS score at 5-7 days or discharge if earlier, from baseline, median (IQR) [d] | -5 (-10 to -2) | -5 (-9 to -1) | | | | |
| EQ-5D-5L score at 90 days, no. of wins/total no. of pairs (%) [f] | 30923/70756 (43.7) | 27899/70756 (39.4) | | WR: 1.11 (0.88 to 1.40) | WR: 1.11 (0.88 to 1.40) | 0.38 |
| EQ-5D-5L score at 90 days, median (IQR) | 0.7 (-0.3 to 1.0) | 0.6 (-0.2 to 1.0) | | | | |
| **Primary safety outcomes** | | | | | | |
| Death within 90 days | 49 (18.4) | 46 (17.3) | | HR: 1.07 (0.71 to 1.60) | HR: 1.06 (0.71 to 1.59) | 0.77 |
| Symptomatic intracranial hemorrhage within 48h [d, g] | 11 (4.1) | 11 (4.1) | 0% (-3.37% to 3.37%) | RR: 1.00 (0.44 to 2.27) | RR: 1.05 (0.45 to 2.44) | 0.91 |
| **Secondary safety outcomes** | | | | | | |
| Any radiologic intracranial hemorrhage within 48h [d] | 69 (25.8) | 66 (24.7) | 1.12% (-6.25% to 8.50%) | RR: 1.05 (0.78 to 1.40) | RR: 1.10 (0.82 to 1.47) | 0.52 |
| Systemic Bleeding [d, h] | | | | | | 0.25 [i] |

| | | |
|---|---|---|
| Mild | 35 (13.1) | 25 (9.4) |
| Moderate | 0 (0.0) | 2 (0.7) |
| Severe | 72 (27.0) | 69 (25.8) |

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 to be 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 and 1 patient in intra-arterial urokinase group.

[c] The Win proportion was calculated by the number of wins in the intra-arterial urokinase group over the control group in mRS among all possible pairs of mRS taking one patient from the intra-arterial urokinase 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. The GenOR indicated the probability of modified Rankin Scale score was lower than the other group. Data for modified Rankin Scale score was missing for 1 patient in the control group and 1 patient in intra-arterial urokinase group.

[d] All outcomes assessed within the first 7 days are analyzed in 267 patients in each treatment group, including the 1 patient in each group who was lost to follow-up between 1 week and 90 days

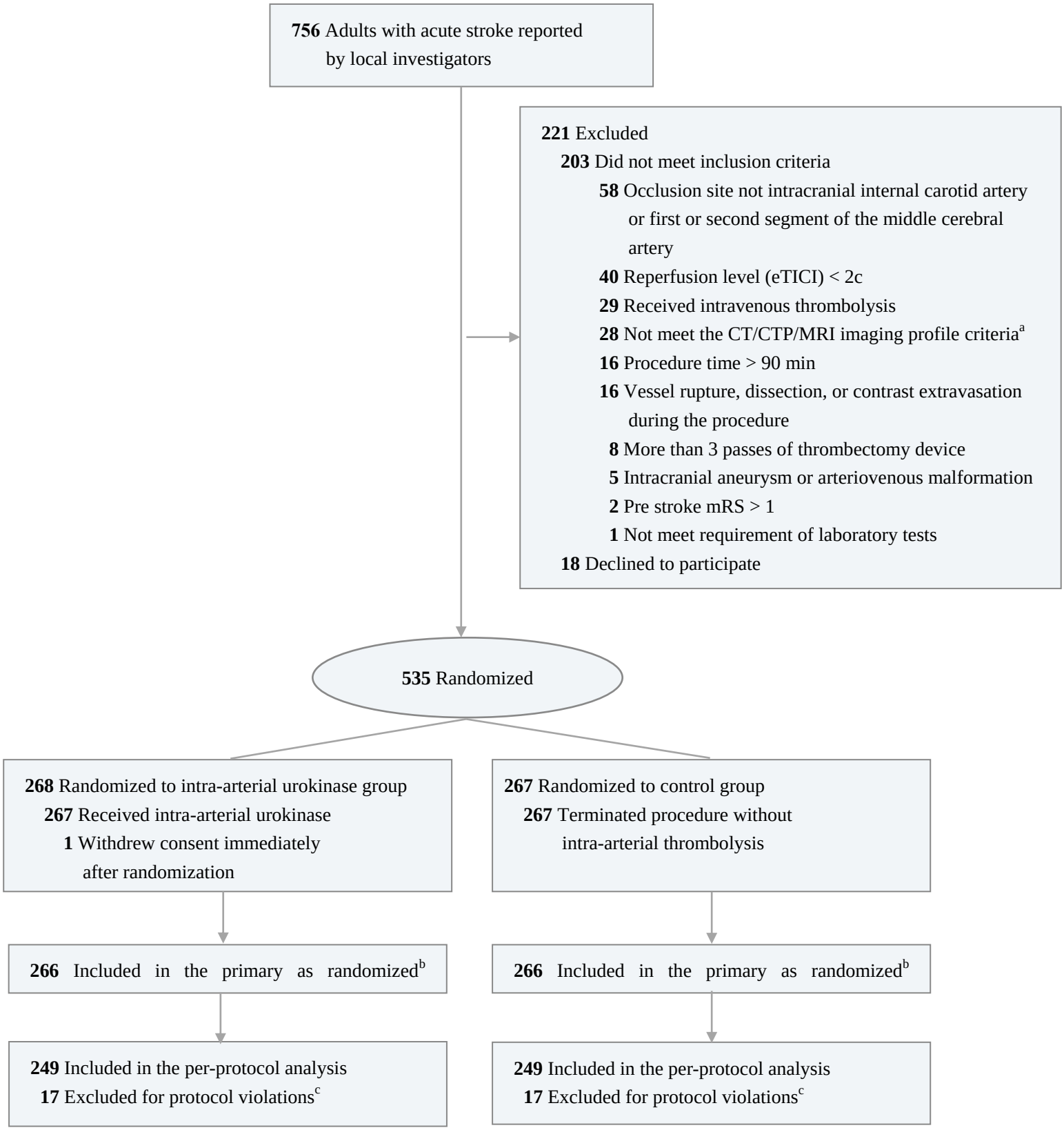
[e] Scores on the NIHSS range from 0 to 42, with higher values reflecting more severe neurologic impairment.

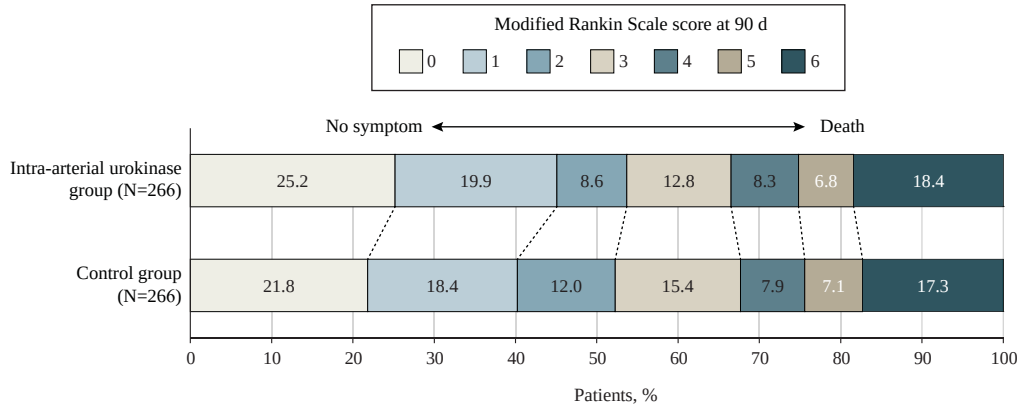
[f] The EQ-5D-5L is a continuous scale measure of self-reported quality of life. Scores range from -0.39 to 1, with lower scores indicating a worse quality of life. Data was missing for 1 patient in the control group and 1 patient in intra-arterial urokinase group.

[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).

[h] 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).

[i] Chi-square Test.


**756** Adults with acute stroke reported by local investigators
**221** Excluded
**203** Did not meet inclusion criteria
**58** Occlusion site not intracranial internal carotid artery or first or second segment of the middle cerebral artery
**40** Reperfusion level (eTICI) < 2c
**29** Received intravenous thrombolysis
**28** Not meet the CT/CTP/MRI imaging profile criteria[a]
**16** Procedure time > 90 min
**16** Vessel rupture, dissection, or contrast extravasation during the procedure
**8** More than 3 passes of thrombectomy device
**5** Intracranial aneurysm or arteriovenous malformation
**2** Pre stroke mRS > 1
**1** Not meet requirement of laboratory tests
**18** Declined to participate
**535** Randomized
**268** Randomized to intra-arterial urokinase group
**267** Received intra-arterial urokinase
**1** Withdrew consent immediately after randomization
**267** Randomized to control group
**267** Terminated procedure without intra-arterial thrombolysis
**266** Included in the primary as randomized[b]
**266** Included in the primary as randomized[b]
**249** Included in the per-protocol analysis
**17** Excluded for protocol violations[c]
**249** Included in the per-protocol analysis
**17** Excluded for protocol violations[c]


Modified Rankin Scale score at 90 d
0
1
2
3
4
5
6
No symptom
Death
Intra-arterial urokinase group (N=266)
25.2
19.9
8.6
12.8
8.3
6.8
18.4
Control group (N=266)
21.8
18.4
12.0
15.4
7.9
7.1
17.3
0
10
20
30
40
50
60
70
80
90
100
Patients, %

| Subgroup | Intra-arterial Urokinase | Control | Adjusted RR (95% CI) | P Value for Interaction |
|---|---|---|---|---|
| | *no. with mRS score of 0 or 1 at 90 days/total no. (%)* | | | |
| **Overall** | 120/266 (45.1) | 107/266 (40.2) | 1.13 (0.94 – 1.36) | |
| **Age, y** | | | | **0.91** |
| ≤ 69 | 68/135 (50.4) | 69/147 (46.9) | 1.11 (0.88 – 1.39) | |
| > 69 | 52/131 (39.7) | 38/119 (31.9) | 1.15 (0.84 – 1.58) | |
| **Sex** | | | | **0.06** |
| Female | 49/105 (46.7) | 38/118 (32.2) | 1.47 (1.07 – 2.02) | |
| Male | 71/161 (44.1) | 69/148 (46.6) | 0.97 (0.77 – 1.22) | |
| **Baseline NIHSS score[a]** | | | | **0.45** |
| ≤ 15 | 81/144 (56.3) | 77/145 (53.1) | 1.08 (0.88 – 1.32) | |
| > 15 | 39/122 (32.0) | 30/121 (24.8) | 1.16 (0.79 – 1.72) | |
| **Prestroke mRS score[b]** | | | | **0.82** |
| 0 | 118/255 (46.3) | 105/254 (41.3) | 1.14 (0.95 – 1.37) | |
| 1 | 2/9 (22.2) | 2/11 (18.2) | 1.01 (0.15 – 6.57) | |
| **Baseline ASPECTS[c]** | | | | **0.40** |
| ≤ 8 | 62/163 (38.0) | 61/162 (37.7) | 1.01 (0.78 – 1.3) | |
| > 8 | 58/103 (56.3) | 46/104 (44.2) | 1.26 (0.96 – 1.63) | |
| **Time from LKW to randomization, min** | | | | **0.51** |
| ≤ 524 | 60/134 (44.8) | 49/133 (36.8) | 1.23 (0.93 – 1.63) | |
| > 524 | 60/132 (45.5) | 58/133 (43.6) | 1.08 (0.84 – 1.39) | |
| **Stroke Etiology[d]** | | | | **0.10** |
| Large Artery Atherosclerosis | 59/135 (43.7) | 60/130 (46.2) | 0.95 (0.74 – 1.23) | |
| Cardioembolism | 48/103 (46.6) | 34/106 (32.1) | 1.49 (1.08 – 2.06) | |
| Other and Unknown | 13/28 (46.4) | 13/30 (43.3) | 1.25 (0.7 – 2.24) | |
| **Occlusion site** | | | | **0.77** |
| ICA | 22/57 (38.6) | 26/67 (38.8) | 0.96 (0.63 – 1.47) | |
| M1 | 71/160 (44.4) | 56/148 (37.8) | 1.15 (0.89 – 1.48) | |
| M2 | 27/49 (55.1) | 25/51 (49.0) | 1.25 (0.87 – 1.79) | |
| **eTICI[e]** | | | | **0.77** |
| 2c | 43/96 (44.8) | 33/90 (36.7) | 1.18 (0.84 – 1.65) | |
| 3 | 76/168 (45.2) | 73/174 (42.0) | 1.11 (0.89 – 1.39) | |