Journal of Neurology (2025) 272:324
https://doi.org/10.1007/s00415-025-13084-2

ORIGINAL COMMUNICATION

Tenecteplase compared to alteplase before mechanical thrombectomy enhances 1-h recanalization and reduces disability in large-vessel occlusion

Lu Wang[1] · Jialu Li[1] · Xiao Wu[1] · Lulan Li[1] · Xueqiao Jiao[1] · Fengyuan Che[2] · Hongxing Han[2] · Liyong Zhang[3] · Weidong Liu[3] · Peifu Wang[4] · Fuxia Yang[1] · Fangfang Zhang[1] · Xunming Ji[1] · Xiuhai Guo[1,5]

Received: 15 February 2025 / Revised: 31 March 2025 / Accepted: 2 April 2025

Abstract

Background The comparative efficacy of tenecteplase versus alteplase in achieving early recanalization (ER) before mechanical thrombectomy (MT) for large-vessel occlusion (LVO) remains uncertain.

Methods This study was a retrospective analysis of prospectively collected data of consecutive patients with LVO underwent intravenous thrombolysis (IVT) and brain angiography between January 2022 and December 2023. ER was defined as ≥50% reperfusion or absence of retrievable thrombus on initial angiography.

Results 146 patients received tenecteplase and 307 received alteplase. Tenecteplase shortened door-to-IVT time (33 vs. 39 min, $P < 0.001$) and door-to-puncture time (97 vs. 109 min, $P = 0.039$) compared to alteplase. Overall ER rates did not differ significantly (17.1% vs. 12.1%, $P = 0.223$). However, a significant interaction was observed between thrombolytic agent and IVT-to-puncture time ($P_{interaction} = 0.034$): tenecteplase achieved higher ER rates when IVT-to-puncture time was < 60 min (17.2% vs. 5.0%, aOR, 4.13 [95% CI 1.24–13.74]). With IVT-to-puncture time ≥ 60 min, ER rates were similar (17.2% vs. 16.8%, aOR 0.91 [95% CI 0.43–1.91]). No ER differences were noted across occlusion sites, clot burden, NIHSS, sex, and age. At 3 months, tenecteplase reduced disability rates (mRS 0–3: 73.5% vs. 65.7%, $P = 0.041$). Functional independence (mRS 0–2) was 57.4% with tenecteplase and 53.1% with alteplase ($P = 0.301$).

Conclusions Real-world observations reveal tenecteplase has increased ER rates compared to alteplase within 1 h of IVT and reduced disability in LVO patients. Further randomized trials are warranted to evaluate the effect of tenecteplase rapid bridging mechanical thrombectomy.

Keywords Tenecteplase · Alteplase · Stroke · Large-vessel occlusion · Bridging therapy

Introduction

Intravenous thrombolysis (IVT) bridging mechanical thrombectomy (MT) is recommended within 4.5 h of symptom onset for acute large-vessel occlusion (LVO) [1], as early recanalization (ER) induced by IVT significantly impacts patient functional outcomes [2, 3]. Despite its widespread use, alteplase achieves early recanalization (ER) in only around 10% of cases [4–7], with efficacy influenced by IVT-to-puncture time, occlusion site, and thrombus characteristics [8–10]. Therefore, the use of novel agents and the exploration of optimal application scenarios are crucial for the treatment of LVO.

Tenecteplase, a genetically modified fibrinogen activator, has high resistance to plasminogen activator inhibitor- 1 and a long half-life, allowing for single-bolus administration

✉ Xiuhai Guo
guoxhxuan@126.com

1 Department of Neurology, Xuanwu Hospital, Capital Medical University, No.45 Changchun Street, Xicheng District, Beijing 100053, China

2 Department of Neurology, Linyi People's Hospital, Linyi, China

3 Department of Neurosurgery, Liaocheng People's Hospital, Liaocheng, China

4 Department of Neurology, Aerospace Center Hospital, Beijing, China

5 Hypoxia Conditioning Translational Laboratory of Clinical Medicine, Capital Medical University, Beijing, China

Published online: 09 April 2025

[11]. In contrast, alteplase requires a 60-min infusion [12]. The EXTEND-IA TNK trial reported higher ER rates and better functional outcomes with tenecteplase versus alteplase in patients with LVO [7]. However, study analyzing patients transferred between hospitals for endovascular therapy have shown similar ER and functional independence between the two agents [13]. This discrepancy may arise from variations in workflow efficiency: alteplase-induced ER increases with prolonged IVT-to-puncture intervals [9, 10], whereas tenecteplase maintains stable ER rates regardless of time [14]. However, limited data are available to assess whether the two thrombolytic agents demonstrate differential ER rates across various IVT-to-puncture time frames. In addition, the relationship between tenecteplase-associated ER and thrombus characteristics, as well as the influence of tenecteplase on thrombus migration, has yet to be fully explored.

In this study, we compared the ER rates in patients with large-vessel occlusion treated with alteplase or tenecteplase. We hypothesized that the efficacy of tenecteplase in improving ER rates is time-dependent and aim to determine the optimal window for the increased recanalization rate of tenecteplase. We also sought to evaluate the potential impact of additional ER predictors such as occlusion site, clot burden score, sex, age, and NIHSS.

Methods

Study population

In this multicenter retrospective study, we evaluated consecutive patients with LVO treated with IVT at three comprehensive stroke centers in China—Linyi People's Hospital, Liaocheng People's Hospital, and Aerospace Center Hospital—between January 2022 and December 2023. All three centers have an annual thrombolysis volume exceeding 200 cases and maintain a uniform prospective registry for the study of IVT in acute ischemic stroke. Patients were eligible for endovascular therapy when a proximal intracranial arterial occlusion was identified according to the latest international guidelines.

Patients who met the following criteria were included: (1) aged 18 and older, (2) baseline CT angiography (CTA) or MR angiography (MRA) shows occlusion in the internal carotid artery (ICA), the first (M1) or second (M2) segment of the middle cerebral artery, or the basilar artery (BA), (3) symptom onset $\leq$4.5 h, or a mismatch on CT perfusion (CTP) or MRI between diffusion-weighted imaging and fluid-attenuated inversion recovery when onset time was unknown, and (4) received IVT with 0.25 mg/kg tenecteplase or 0.9 mg/kg alteplase and a brain digital subtraction angiography (DSA).

The exclusion criteria were: extra-cranial carotid occlusion, multiple sites occlusion, missing critical imaging data or critical information, and IVT-to-puncture time more than 8 h.

Data collection

Data were obtained from the registry and supplemented by reviewing medical records when necessary: age, sex, baseline and 24 h National Institutes of Health Stroke Scale (NIHSS), medical history (including hypertension, hyperlipidemia, diabetes, coronary heart disease, atrial fibrillation, previous stroke, antiplatelets use, and smoking), and time points (symptom onset, hospital arrival, IVT, groin puncture, and recanalization).

All patients received a non-contrast CT scan, either CTA or MRA at baseline, followed by subsequent DSA imaging assessments. All patient imaging was independently evaluated by two experienced radiologists at each center, who were blinded to the procedure and clinical outcomes. The following data were recorded: (1) intracranial occlusion site was identified on baseline CTA or MRA with the following categorizations: ICA, M1, M2, or BA; (2) clot burden was assessed using the clot burden score on CTA or MRA images [15]; (3) modified thrombolysis in cerebral infarction (mTICI) grade was evaluated on initial and finally DSA; (4) occlusion site on the first intracranial DSA.

Definition of outcome variables

Clinical outcomes were evaluated using the NIHSS at 24 h and the modified Rankin Scale (mRS) at 3 months. Early clinical improvement is defined as a reduction of the NIHSS score by $\geq$8 or achieving an NIHSS score of 0–1 at 24-h post-treatment; functional independence is defined as mRS 0–2 at 3 months. The 3-month mRS scores were determined by neurologists through telephone interviews or routine outpatient clinic visits. Care pathway information was blinded to the assessors collecting the clinical outcome data.

Early recanalization was defined as mTICI of 2b–3 (reperfusion has occurred in over 50% of the affected zone) or the absence of a retrievable thrombus on the initial DSA. We also assessed partial recanalization, defined as mTICI of 2a (reperfusion has occurred in $<$50% of the affected zone). Thrombus migration was characterized as a change to a more distal occlusion on the angiogram compared to the initial occlusion on the CTA. The initial occlusion was identified as the thrombus's most proximal location on the CTA. On the angiogram, occlusion was determined as the thrombus's most proximal location on the initial DSA.

Safety outcomes were assessed, including: parenchymal hematomas 2 (PH- 2), defined according to the ECASS II criteria [16]; symptomatic intracranial hemorrhage (sICH)

defined according to the SITS-MOST criteria [17]; and mortality, defined as an mRS score of 6.

Statistical analysis

Quantitative variables were represented by the median and interquartile range, while qualitative variables were expressed as frequency and percentage. The χ^2 test, Fisher's exact test, and Mann–Whitney *U* test were applied as appropriate for assessing baseline and outcome variables. The primary imaging outcome, early recanalization rates of tenecteplase and alteplase, was assessed while adjusting for baseline NIHSS score, age, occlusion site, and time from hospital arrival to puncture. Then, we evaluated primary imaging outcomes within subgroups categorized by sex (male, female), age (< 80, ≥ 80 years), NIHSS (< 15, ≥ 15), IVT-to-puncture time (< 60 and ≥ 60 min), occlusion site (ICA, M1, M2, and BA), and clot burden score (0–4, 5–7, and ≥ 8), while adjusting for pertinent covariates using logistic regression models and calculating *P* values for interaction ($P_{interaction}$). Furthermore, restricted cubic splines were utilized to examine the possible nonlinear relationship between IVT-to-puncture time and early recanalization. We compared the 3-month mRS scores in two treatment groups for clinical outcomes by adjusting for baseline NIHSS score, age, and time from symptom onset to IVT. All *P* values reported are two-sided, with significance defined as $P < 0.05$. Statistical analysis was conducted with IBM SPSS version 27 and R statistics software version 4.2.2.

Results

During the study period, 533 patients with large-vessel occlusion who underwent intravenous thrombolysis and brain angiography were admitted to the participating centers. Among them, 14 received urokinase-type plasminogen activator, 364 received alteplase, and 155 received tenecteplase. After excluding 66 patients for the following reasons—6 with CTA from external hospital not available, 22 missing DSA data, 14 missing CTA data, 16 with standalone cervical ICA occlusion, 3 with anterior cerebral artery occlusion, 2 with posterior cerebral artery occlusion, and 3 with vertebral artery occlusion—the final analysis included 453 patients: 307 in the alteplase group and 146 in the tenecteplase group. Furthermore, 3-month mRS data were missing for 10 patients in the tenecteplase group and 36 in the alteplase group (Fig. 1).

Table 1 presents the baseline characteristics of patients in each treatment group. Contrasting the tenecteplase and alteplase groups, age, sex, medical history, baseline NIHSS score, occlusion site, and clot burden score were equally distributed. Occlusions most commonly occurred at the ICA (37.3%) and M1 segment (36.9%). Administration of tenecteplase resulted in a significantly reduced time from hospital arrival to intravenous thrombolysis (median 33 min, IQR 24–42 vs. alteplase median 39 min, IQR 30–49, $P < 0.001$) and time from hospital arrival to puncture (median 97 min, IQR 84–125 vs. alteplase median 109 min, IQR 88–141, $P = 0.039$). The times from symptom onset to hospital arrival, from symptom onset to intravenous thrombolysis, from intravenous thrombolysis to puncture, and from puncture to recanalization were similar between the groups.

ER occurred in 37 patients (12.1%) treated with alteplase and 25 patients (17.1%) treated with tenecteplase (aOR, 1.45 [95% CI 0.80–2.64]; $P = 0.223$) (Table 2). Subgroup analysis revealed no significant differential impact on ER rates across various factors, including sex ($P_{interaction} = 0.678$), age ($P_{interaction} = 0.109$), NIHSS ($P_{interaction} = 0.546$), clot burden score ($P_{interaction} = 0.469$), and occlusion site ($P_{interaction} = 0.908$) (Table 3). According to IVT-to-puncture time (< 60 vs. ≥ 60 min), tenecteplase and alteplase had differing effects on ER rates ($P_{interaction} = 0.034$). Within 60 min of IVT-to-puncture time, ER rates were higher with tenecteplase compared to alteplase (tenecteplase: 17.2% vs. alteplase: 5.0%, aOR, 4.13 [95% CI, 1.24–13.74]). In contrast, there was no difference between the two groups when the IVT-to-puncture time was more than 60 min (tenecteplase: 17.2% vs. alteplase: 16.8%, aOR, 0.91 [95% CI 0.43–1.91]) (Table 3). Multivariable adjusted restricted cubic spline analyses indicated a nonlinear relationship between IVT-to-puncture time and ER achieved with alteplase ($P = 0.004$) (Fig. 2A). aORs increased significantly with longer IVT-to-puncture time until approximately 113 min (aOR per SD = 2.11, [95% CI 1.38–3.23]). No such relationships were found in the tenecteplase group ($P = 0.333$) (Fig. 2B). The detailed ER rates for the two groups under different IVT-to-puncture time intervals are shown in the Online Resource 1.

Thrombus migration was observed in 28 of 146 cases (19.1%) in the tenecteplase group and 38 of 307 cases (12.3%) in the alteplase group ($P = 0.055$). Among cases with thrombus migration, early recanalization rates were similar between groups (tenecteplase: 42.9% vs alteplase: 42.1%, $P = 0.879$), while partial recanalization occurred more frequently in the tenecteplase group (17.9%) than in the alteplase group (10.5%) ($P = 0.396$). Detailed patterns of thrombus migration and their relationship to reperfusion status are presented in Table 4.

The post-MT recanalization rates and early clinical improvement rates were similar between the groups. Rates of PH- 2, sICH, and mortality (mRS 6) were also comparable between the alteplase and tenecteplase groups (Table 2). After adjusting for relevant covariates, we analyzed the modified Rankin scale (mRS) score at 3-month. Patients receiving tenecteplase had a significantly higher rate of recovery to independent or mildly disabled function (mRS

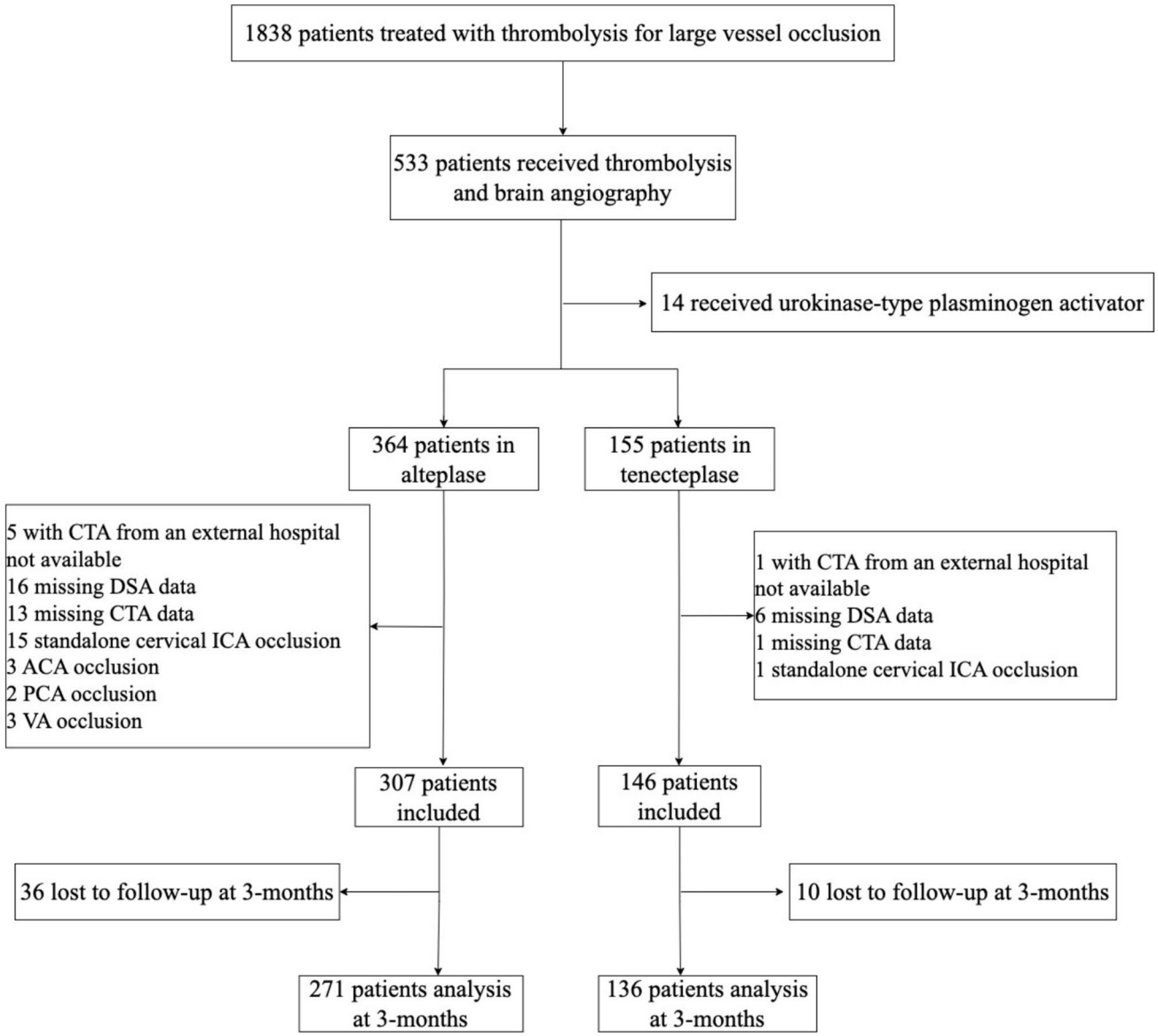

Fig. 1 Flow diagram of the study inclusion and exclusion. *CTA* CT angiography, *DSA* digital subtraction angiography, *ICA* internal carotid artery, *ACA* anterior cerebral artery, *PCA* posterior cerebral artery, *VA* vertebral artery

0–3), with 100/136 (73.5%) patients compared to 178/271 (65.7%) patients in the alteplase group (aOR, 1.69; [95% CI 1.02–2.80]; $P = 0.041$). Mortality rates were similar between the groups (10.3% vs. 16.2%, aOR, 0.59; [95% CI 0.31–1.12]; $P = 0.109$). Functional independence (mRS 0–2) at 3-month was achieved by 80/136 (57.4%) patients in the tenecteplase group and 148/271 (53.1%) patients in the alteplase group (aOR, 1.26; [95% CI 0.81–2.00]; $P = 0.301$) (Table 2). Further comparison of 3-month functional independence between the two thrombolytic drugs was performed in the IVT-to-puncture time subgroups. In the cohort with an IVT-to-puncture time < 60 min, the incidence of functional independence was 50.5% with alteplase and 60.0% with tenecteplase (aOR, 1.47; [95% CI 0.75–2.90]; $P = 0.262$). In the group with an IVT-to-puncture time ≥ 60 min, the incidence of functional independence was 55.3% with alteplase and 56.5% with tenecteplase (aOR, 1.05; [95% CI 0.62–1.78]; $P = 0.866$) (Fig. 3).

Discussion

Our findings indicate that tenecteplase is significantly more effective than alteplase in achieving early recanalization when the IVT-to-puncture time is under 1 h. In addition, tenecteplase also leads to a higher rate of recovery

Table 1 Baseline characteristics

	Alteplase ($n = 307$)	Tenecteplase ($n = 146$)	*P* value
Age, *year*; median (IQR)	68 (58–75)	69 (60–75)	0.219
Male, *n* (%)	203 (66.1%)	95 (65.1%)	0.825
NIHSS, median (IQR)	17 (13–20)	16 (12–20)	0.892
Medical history, *n* (%)			
Hypertension	227 (73.9%)	100 (68.5%)	0.226
Hyperlipidemia	66 (21.5%)	30 (20.6%)	0.817
Diabetes	66 (21.5%)	38 (26.0%)	0.284
Coronary heart disease	75 (24.4%)	36 (24.7%)	0.958
Atrial fibrillation	73 (23.8%)	36 (24.7%)	0.838
Previous stroke	65 (21.2%)	37 (25.3%)	0.321
Antiplatelets	63 (20.5%)	34 (24.0%)	0.404
Current smoking	95 (30.9%)	42 (29.0%)	0.669
Site of occlusion, *n* (%)			
ICA	118 (38.4%)	51 (34.9%)	0.214
M1	115 (37.5%)	52 (35.6%)	
M2	23 (7.5%)	20 (13.7%)	
BA	51 (16.6%)	23 (15.8%)	
Clot burden score, *n* (%)			
0–4	96 (31.3%)	58 (39.7%)	0.184
5–7	124 (40.4%)	49 (33.6%)	
8–10	87 (28.3%)	39 (26.7%)	
Workflow times, min; median (IQR)			
Stroke symptom onset to hospital arrival[a]	120 (60–176)	120 (77–172)	0.674
Stroke symptom onset to IVT[b]	155 (105–210)	152 (106–206)	0.649
Hospital arrival to IVT[c]	39 (30–49)	33 (24–42)	< 0.001
Stroke symptom onset to puncture[d]	240(175–300)	220 (180–281)	0.386
Hospital arrival to puncture[e]	109 (88–141)	97 (84–125)	0.039
Thrombolysis to puncture[f]	68 (49–95)	66 (50–89)	0.843
Puncture to recanalization[g]	35 (26–57)	50 (30–72)	0.005

Number of missing values: a5, b4, c8, d1, e5, f3, g55

IQR interquartile range; *NIHSS* National Institutes of Health Stroke Scale; *mRS* modified Rankin Scale; *IVT* intravenous thrombolysis

to independent or mildly disabled function (mRS 0–3) at 3 months. Furthermore, the administration of tenecteplase significantly reduced the time from hospital arrival to the initiation of thrombolysis and thrombectomy.

Our analysis of ER rates, with a median IVT-to-puncture time of 67 min, shows the similarity between the tenecteplase and alteplase groups, with ER rates of 17.1% and 12.1%, respectively. This observation is consistent with the ER rates from previous studies that reported longer IVT-to-puncture times, demonstrating rates of 19.8% versus 18.5% with a median evaluation time of 88 min [18], and 21% versus 18% with 93 min [13]. In the EXTEND-IA-TNK trial, a shorter IVT to arterial puncture time (median of 43 min) showed significantly higher ER rates for tenecteplase compared to alteplase (22% vs. 10%) [7]. However, in the AcT trial, also with shorter IVT to reperfusion assessment time (median of 53 min), ER rates were around 10%, with no significant differences between tenecteplase and alteplase [19]. Prior studies have provided inconsistent findings and did not stratify recanalization rates based on IVT-to-puncture time intervals. Our analysis suggests a trend of progressively decreasing disparity in recanalization rates between tenecteplase and alteplase as IVT-to-puncture times increased, until no significant difference remained.

Our analysis demonstrates a superior recanalization efficacy of tenecteplase when the IVT-to-puncture time is restricted to around 1 h. This significant difference can be attributed to the distinct pharmacological mechanisms of the two drugs. Tenecteplase has a prolonged half-life of 20 min and reaches maximum concentration within 1 min following a single bolus [11, 20]. After 60 min post-IVT, tenecteplase has completed three half-life cycles, resulting

Table 2 Outcomes

	Alteplase ($n = 307$)	Tenecteplase ($n = 146$)	P value
Early recanalization before MT, *n* (%)	37 (12.1%)	25 (17.1%)	0.223
mTICI 0	238 (77.5%)	101 (69.1%)	
mTICI 1	24 (7.8%)	12 (8.2%)	
mTICI 2a	8 (2.6%)	8 (5.4%)	
mTICI 2b	27 (8.7%)	17 (11.6%)	
mTICI 3	10 (3.2%)	8 (5.4%)	
Thrombus migration, *n* (%)	38 (12.3%)	28 (19.1%)	0.055
Post-MT recanalization, *n* (%)[a]	244 (90.4%)	102 (88.7%)	0.618
mTICI 0	9 (3.3%)	2 (1.7%)	
mTICI 1	10 (3.4%)	6 (5.2%)	
mTICI 2a	7 (2.6%)	5 (4.4%)	
mTICI 2b	39 (14.4%)	18 (15.7%)	
mTICI 3	205 (75.9%)	84 (73.0%)	
Early clinical improvement, *n* (%)	74 (24.1%)	39 (26.7%)	0.549
PH- 2, *n* (%)	35 (11.4%)	14 (9.6%)	0.562
sICH, *n* (%)	10 (3.3%)	8 (5.5%)	0.258
Functional outcome at 90 days[b]			
mRS score 0–2, *n* (%)	144 (53.1%)	78 (57.4%)	0.301
mRS score 0–3, *n* (%)	178 (65.7%)	100 (73.5%)	0.041
mRS score 6, *n* (%)	44 (16.24%)	14 (10.29%)	0.106

[a]Assessed in patients were not recanalized before thrombectomy, 121 and 270 patients in the tenecteplase and alteplase groups

[b]Endpoint not available in 10 and 36 patients in the tenecteplase and alteplase groups, respectively

PH parenchymal hematoma, *sICH* symptomatic intracranial hemorrhage, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale

Table 3 Effects of tenecteplase compared to alteplase on early recanalization rates in the prespecified subgroup

	Alteplase ($n = 307$)	Tenecteplase ($n = 146$)	aOR (95% CI)	$P_{\text{interaction}}$
Sex				
Male	25/202 (12.4%)	15/91 (16.5%)	1.38 (0.65–2.95)	0.678
Female	12/104 (11.5%)	10/51 (19.6%)	1.55 (0.56–4.26)	
Age (years)				0.109
< 80	36/278 (12.9%)	22/126 (17.5%)	1.26 (0.68–2.36)	
≥ 80	1/28 (3.6%)	3/16 (18.8%)	19.50 (0.75–509.56)	
NIHSS				0.546
< 15	12/108 (11.1%)	14/57 (24.6%)	1.62 (0.61–4.34)	
≥ 15	25/199 (12.6%)	11/89 (12.4%)	1.16 (0.49–2.77)	
Clot burden score				0.469
0–4	5/96 (5.3%)	3/56 (5.4%)	1.76 (0.26–12.01)	
5–7	16/124 (12.9%)	8/48 (16.7%)	1.23 (0.46–3.28)	
8–10	16/87 (18.4%)	14/38 (36.8%)	2.21 (0.85–5.74)	
Occlusion site				0.908
ICA	5/118 (4.2%)	2/49 (4.1%)	0.91 (0.16–5.25)	
M1	23/115 (20.0%)	15/52 (28.8%)	1.60 (0.74–3.45)	
M2	8/23 (34.8%)	7/19 (36.8%)	1.48 (0.37–5.88)	
BA	1/50 (2.0%)	1/22 (4.5%)	3.02 (0.14–65.34)	
IVT-to-puncture time (min)				0.034
< 60 min	6/121 (5.0%)	10/58 (17.2%)	4.13 (1.24–13.74)	
≥ 60 min	31/184 (16.8%)	15/87 (17.2%)	0.91 (0.43–1.91)	

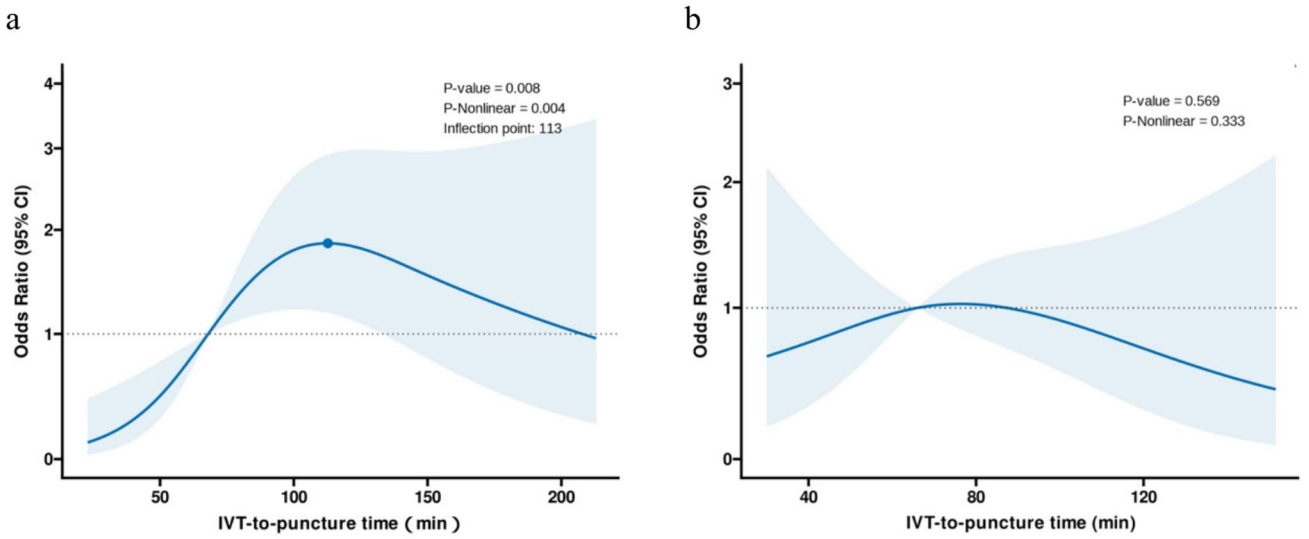

Fig. 2 Association of IVT-to-puncture time with pre-MT recanalization in a restricted cubic spline model. **a** Alteplase group; **b** tenecteplase group. aORs, solid line; 95% CI, shadows

Table 4 Thrombus migration patterns and recanalization status achieved with thrombolysis (alteplase or tenecteplase)

	Alteplase			Tenecteplase		
	Early recanalization (16)	Partial recanalization (4)	No change (18)	Early recanalization (12)	Partial recanalization (5)	No change (11)
ICA → distal ICA			2 (11%)		1 (20%)	
ICA → M1		2 (50%)	3 (17%)		1 (20%)	3 (27%)
ICA → M2	1 (6%)		1 (6%)			
ICA → distal occlusion (M3 and beyond)			1 (6%)	2 (17%)		
Proximal M1 → distal M1	2 (13%)					1 (9%)
M1 (proximal or distal) → M2	2 (13%)		8 (44%)	2 (17%)	2 (40%)	4 (36%)
M1 (proximal or distal) → distal occlusion (M3 and beyond)	7 (44%)	1 (25%)		5 (42%)	1 (20%)	
M2 → distal occlusion (M3 and beyond)	3 (19%)	1 (25%)	2 (11%)	3 (25%)		1 (9%)
BA → P1 or P2	1 (6%)		1 (6%)			2 (18%)

in a concentration of only 0.03 mg/kg. In contrast, alteplase has a short half-life of only 5 min and is rapidly metabolized and cleared after a 60-min infusion [21, 22]. Consequently, the therapeutic effectiveness of both thrombolytic agents diminishes substantially after 1 h. In the alteplase group, any further increase in recanalization rates observed 1 h post-thrombolysis is likely due to spontaneous recanalization rather than the direct effect of the drug [5, 6]. Conversely, tenecteplase has a high resistance to plasminogen activator inhibitor- 1 activity, which enhances its thrombolytic capacity, facilitating rapid recanalization within 1 h in patients with the potential for spontaneous recanalization [23]. Therefore, an IVT-to-puncture time exceeding 1 h can be considered "pseudo-bridging," which is an ineffective waiting period both for alteplase and tenecteplase. Timely bridging to endovascular treatment is to maximize the therapeutic efficacy of both thrombolytic agents.

In our study, we assessed the impact of occlusion location and clot burden on the efficacy of tenecteplase and alteplase in achieving recanalization for large-vessel occlusion. We found both tenecteplase and alteplase are generally ineffective in achieving recanalization in cases of ICA or basilar artery occlusion and high clot burden. Conversely, for small vessel occlusions, the TRACE- 2 trial demonstrated that both drugs were effective in moderate acute ischemic stroke patients who did not receive mechanical thrombectomy. Favorable outcomes (mRS 0–2) at 90 days was similar for both tenecteplase (73%) and alteplase (72%), showing no

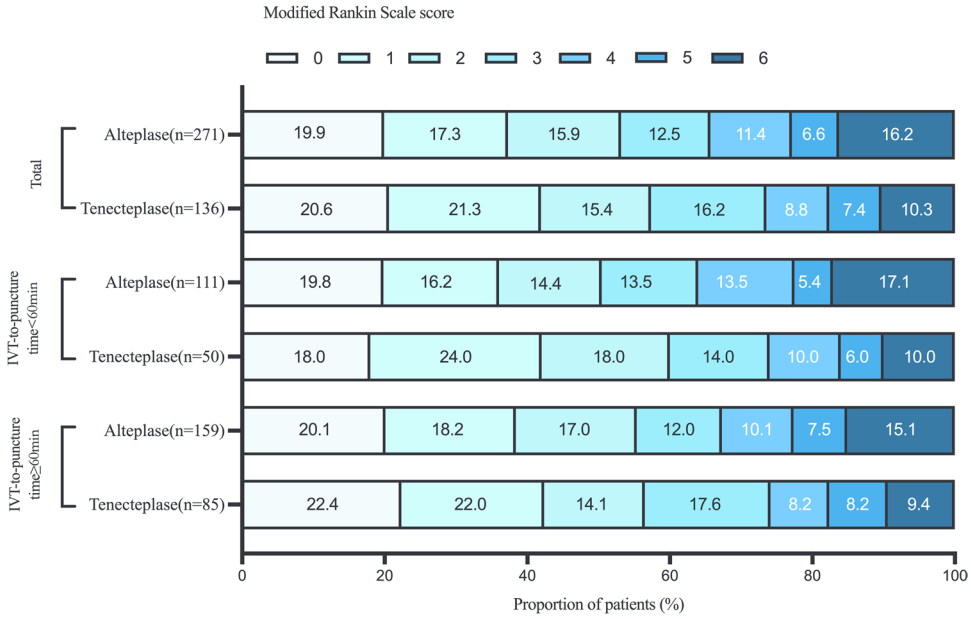

Fig. 3 3-month modified Rankin scale (mRS) scores in tenecteplase and alteplase groups

significant difference in efficacy [24]. However, our findings are limited by a small sample size, which prevented us from detecting a significant difference in recanalization effects between tenecteplase and alteplase, regardless of the occlusion location and clot burden. Table 3 seems to align with the previous report, which indicated superior recanalization rates with tenecteplase in patients with occlusions in the middle cerebral artery and lower clot burden [25]. Furthermore, tenecteplase has been shown to have better functional outcomes than alteplase in a study that primarily included the middle cerebral artery [26]. In conclusion, the effect of tenecteplase and alteplase varies depending on the specific occlusion site and clot characteristics.

In our analysis, we observed a median door-to-needle time of 37 min (IQR 30–47) and a door-to-puncture time of 105 min (IQR 86–136), which are below the Chinese average [27]. Notably, treatment with tenecteplase further decreased the median time from hospital arrival to IVT by 6 min and to puncture by 12 min compared to alteplase. The time savings may be attributed to the simpler administration method of tenecteplase, which is administrated as a single bolus. In contrast, alteplase, being a lyophilized powder, necessitates prior preparation of the solution. In addition, the alteplase bolus is administered only after the entire infusion has been prepared and is ready to be started, immediately following the bolus in our centers. Research has demonstrated that each minute advanced by thrombolysis results in at least an additional day of disability-free life, and each minute advanced by puncture contributes to an additional week of disability-free life [28, 29]. Stroke units globally are persistently engaged in optimizing their care systems, thereby reducing door-to-treatment time [30, 31]. Consequently, as healthcare systems increasingly adopt tenecteplase, this could reduce door-to-treatment time and provide an advantage in bridging MT.

In recent years, several large-sample randomized controlled trials have compared the efficacy of tenecteplase and alteplase in AIS, demonstrating that tenecteplase is non-inferior to alteplase [19, 24, 32, 33]. In addition, some studies have demonstrated that tenecteplase and alteplase have comparable recanalization rates prior to MT in patients with LVO [34, 35]. The advantages of tenecteplase can manifest in specific patient subgroups. Gerschenfeld et al. showed that tenecteplase is associated with better 3-month mRS scores and lower 3-month mortality in patients with large ischemic core compared with alteplase [36]. Checkouri et al. found that tenecteplase has a higher ER rate compared with alteplase in patients with larger thrombi [18]. Our study indicates that tenecteplase is more effective than alteplase in patients with LVO regarding the rapid initiation of endovascular therapy, as it is associated with a significantly higher recanalization rate and improved functional outcomes. Tenecteplase may be preferentially used for patients directly admitted to comprehensive stroke centers. Further research comparing tenecteplase with alteplase in rapid bridging mechanical thrombectomy for large-vessel occlusion is ongoing (ClinicalTrials.gov numbers, NCT06658197). Patients receiving tenecteplase at primary stroke centers or mobile stroke units without MT capabilities should be directly transferred to angiography suites after hospital arrival, bypassing conventional imaging to reduce onset-to-reperfusion time and achieve a favorable outcome [37].

Our study has several limitations. First, it was constrained by a limited sample size and utilized retrospectively collected data, which could potentially lead to the inclusion of unmeasured confounders that might affect the outcomes.

Second, we failed to measure thrombus characteristics, such as thrombus length and permeability. Furthermore, the relatively high rate of loss to follow-up (near 10% at the 3-month mRS) may have weakened the value of our mRS results.

Conclusion

Tenecteplase exhibits enhanced recanalization efficacy in patients with large-vessel occlusion when the duration between intravenous thrombolysis and endovascular puncture is limited to 1 h. Furthermore, it shortens the time from hospital arrival to starting thrombolysis and thrombectomy. These findings further support the preferential use of tenecteplase to rapidly bridge mechanical thrombectomy in patients with large-vessel occlusion.

Acknowledgements This work is supported by the National Science and Technology Major Project (2023ZD0503806), National Nature Science Foundation of China (82171302), and Capital's Funds for Health Improvement and Research (2024 - 1- 2011).

Author contributions LW, XMJ, and XHG conceived and designed the study. FYC, HXH, LYZ, WDL, and PFW contributed to the acquisition of data. LW, JLL, XW, XQJ, LLL, FXY, and FFZ contributed to statistical analyses and interpretation of data. LW and XHG drafted and revised the manuscript for content. All the authors have read and approved the manuscript.

Funding This work was supported by National Science and Technology Major Project, 2023ZD0503806, Xiuhai Guo, National Nature Science Foundation of China, 82171302, Xiuhai Guo, Capital's Funds for Health Improvement and Research, 2024 - 1- 2011, Xiuhai Guo.

Data availability Data collected for the study may be made available from the corresponding author to others upon reasonable request.

Declarations

Conflicts of interest The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval The study adhered to the principles of the Declaration of Helsinki and was conducted with approval from Xuanwu Hospital, Capital Medical University ethics committee (Approval Number: [2021] 215, Approval Date: October 20th, 2021). Informed consent for data collection was obtained from all the participants.

References

1. Berge E, Whiteley W, Audebert H et al (2021) European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. Eur Stroke J 6:I–LXII. https://doi.org/10.1177/2396987321989865
2. Arrarte Terreros N, Bruggeman AAE, Swijnenburg ISJ et al (2022) Early recanalization in large-vessel occlusion stroke patients transferred for endovascular treatment. J Neurointerv Surg 14:480. https://doi.org/10.1136/neurintsurg-2021-017441
3. Rha J-H, Saver JL (2007) The impact of recanalization on ischemic stroke outcome—a meta-analysis. Stroke 38:967–973. https://doi.org/10.1161/01.Str.0000258112.14918.24
4. Tsivgoulis G, Katsanos AH, Schellinger PD et al (2018) Successful reperfusion with intravenous thrombolysis preceding mechanical thrombectomy in large-vessel occlusions. Stroke 49:232. https://doi.org/10.1161/strokeaha.117.019261
5. Lecouffe NE, Kappelhof M, Treurniet KM et al (2021) A randomized trial of intravenous alteplase before endovascular treatment for stroke. N Engl J Med 385:1833–1844. https://doi.org/10.1056/NEJMoa2107727
6. Yang P, Zhang Y, Zhang L et al (2020) Endovascular thrombectomy with or without intravenous alteplase in acute stroke. N Engl J Med 382:1981–1993. https://doi.org/10.1056/NEJMoa2001123
7. Campbell BCV, Mitchell PJ, Churilov L et al (2018) Tenecteplase versus alteplase before thrombectomy for ischemic stroke. N Engl J Med 378:1573–1582. https://doi.org/10.1056/NEJMoa1716405
8. Menon BK, Al-Ajlan FS, Najm M et al (2018) Association of Clinical, imaging, and thrombus characteristics with recanalization of visible intracranial occlusion in patients with acute ischemic stroke. J Am Med Assoc 320:1017–1026. https://doi.org/10.1001/jama.2018.12498
9. Seners P, Turc G, Naggara O et al (2018) Post-thrombolysis recanalization in stroke referrals for thrombectomy incidence, predictors, and prediction scores. Stroke 49:2975–2982. https://doi.org/10.1161/strokeaha.118.022335
10. Zhou Y, Zhang L, Ospel J et al (2022) Association of intravenous alteplase, early reperfusion, and clinical outcome in patients with large vessel occlusion stroke: most hoc analysis of the randomized DIRECT-MT trial. Stroke 53:1828–1836. https://doi.org/10.1161/strokeaha.121.037061
11. Tanswell P, Modi N, Combs D et al (2002) Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. Clin Pharmacokinet 41:1229–1245. https://doi.org/10.2165/00003088-200241150-00001
12. Acheampong P, Ford GA (2012) Pharmacokinetics of alteplase in the treatment of ischaemic stroke. Expert Opin Drug Metab Toxicol 8:271–281. https://doi.org/10.1517/17425255.2012.652615
13. Seners P, Caroff J, Chausson N et al (2019) Recanalization before thrombectomy in tenecteplase vs alteplase-treated drip-and-ship patients. J Stroke 21:105–107. https://doi.org/10.5853/jos.2018.01998
14. Gerschenfeld G, Smadja D, Turc G et al (2021) Functional outcome, recanalization, and hemorrhage rates after large vessel occlusion stroke treated with tenecteplase before thrombectomy. Neurology 97:E2173–E2184. https://doi.org/10.1212/wnl.0000000000012915
15. Tan IYL, Demchuk AM, Hopyan J et al (2009) CT Angiography clot burden score and collateral score: correlation with clinical

and radiologic outcomes in acute middle cerebral artery infarct. Am J Neuroradiol 30:525–531. https://doi.org/10.3174/ajnr.A1408
16. Hacke W, Kaste M, Fieschi C et al (1998) Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 352:1245–1251. https://doi.org/10.1016/s0140-6736(98)08020-9
17. Mazya M (2012) Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe implementation of treatments in stroke (SITS) symptomatic intracerebral hemorrhage risk score (vol 43, pg 1524, 2012). Stroke 43:E102–E102. https://doi.org/10.1161/STR.0b013e318262de57
18. Checkouri T, Gerschenfeld G, Seners P et al (2023) Early recanalization among patients undergoing bridging therapy with tenecteplase or alteplase. Stroke 54:2491–2499. https://doi.org/10.1161/strokeaha.123.042691
19. Menon BK, Buck BH, Singh N et al (2022) Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. Lancet 400:161–169
20. Tang F, Langenhorst J, Dang S et al (2023) Population pharmacokinetics of tenecteplase in patients with acute myocardial infarction and application to patients with acute ischemic stroke. J Clin Pharmacol 63:197–209. https://doi.org/10.1002/jcph.2164
21. Kobayashi Y, Saito T, Kawabata Y et al (2023) A 5-minute delay from bolus injection to infusion halves plasma concentration of tissue plasminogen activator. J Emerg Med 64:709–713. https://doi.org/10.1016/j.jemermed.2023.03.059
22. Smith C, Al-Nuaimi Y, Wainwright J et al (2014) The influence of bolus to infusion delays on plasma tissue plasminogen activator levels. Int J Stroke 9:939–942. https://doi.org/10.1111/j.1747-4949.2012.00924.x
23. Huber K (2001) Plasminogen activator inhibitor type-1 (part two): role for failure of thrombolytic therapy. PAI-1 resistance as a potential benefit for new fibrinolytic agents. J Thromb Thrombolysis 11:195–202. https://doi.org/10.1023/a:1011952602122
24. Wang YJ, Li SY, Pan YS et al (2023) Tenecteplase versus alteplase in acute ischaemic cerebrovascular events (TRACE-2): a phase 3, multicentre, open-label, randomised controlled, non-inferioritytrial. Lancet 401:645–654. https://doi.org/10.1016/s0140-6736(22)02600-9
25. Yogendrakumar V, Churilov L, Guha P et al (2023) Tenecteplase treatment and thrombus characteristics associated with early reperfusion: an EXTEND-IA TNK trials analysis. Stroke 54:706–714. https://doi.org/10.1161/strokeaha.122.041061
26. Parsons M, Spratt N, Bivard A et al (2012) A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med 366:1099–1107. https://doi.org/10.1056/NEJMoa1109842
27. Ye Q, Zhai F, Chao B et al (2022) Rates of intravenous thrombolysis and endovascular therapy for acute ischaemic stroke in China between 2019 and 2020. Lancet Region Health-Western Pacific. https://doi.org/10.1016/j.lanwpc.2022.100406
28. Meretoja A, Keshtkaran M, Tatlisumak T et al (2017) Endovascular therapy for ischemic stroke save a minute-save a week. Neurology 88:2123–2127. https://doi.org/10.1212/wnl.0000000000003981
29. Meretoja A, Keshtkaran M, Saver JL et al (2014) Stroke thrombolysis save a minute, save a day. Stroke 45:1053–1058. https://doi.org/10.1161/strokeaha.113.002910
30. Meretoja A, Weir L, Ugalde M et al (2013) Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. Neurology 81:1071–1076. https://doi.org/10.1212/WNL.0b013e3182a4a4d2
31. Kamal N, Holodinsky JK, Stephenson C et al (2017) Improving door-to-needle times for acute ischemic stroke: effect of rapid patient registration, moving directly to computed tomography, and giving alteplase at the computed tomography scanner. Circ Cardiovasc Qual Outcomes. https://doi.org/10.1161/circoutcomes.116.003242
32. Parsons MW, Yogendrakumar V, Churilov L et al (2024) Tenecteplase versus alteplase for thrombolysis in patients selected by use of perfusion imaging within 4<middle dot>5 h of onset of ischaemic stroke (TASTE): a multicentre, randomised, controlled, phase 3 non-inferiority trial. Lancet Neurol 23:775–786. https://doi.org/10.1016/s1474-4422(24)00206-0
33. Meng X, Li S, Dai H et al (2024) Tenecteplase vs alteplase for patients with acute ischemic stroke. J Am Med Assoc 332:1437–1445. https://doi.org/10.1001/jama.2024.14721
34. Karamchandani RR, Asimos AW, Strong D et al (2024) Early recanalization after tenecteplase versus alteplase: experience in a large stroke network. J Stroke Cerebrovasc Dis. https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.107931
35. Hendrix P, Gross BA, Allahdadian S et al (2024) Tenecteplase versus alteplase before stroke thrombectomy: outcomes after system-wide transitions in Pennsylvania. J Neurol 271:5637–5641. https://doi.org/10.1007/s00415-024-12530-x
36. Gerschenfeld G, Turc G, Obadia M et al (2024) Functional outcome and hemorrhage rates after bridging therapy with tenecteplase or alteplase in patients with large ischemic core. Neurology. https://doi.org/10.1212/wnl.0000000000209398
37. Ribo M, Molina CA, Cobo E et al (2016) Association between time to reperfusion and outcome is primarily driven by the time from imaging to reperfusion. Stroke 47:999–1004. https://doi.org/10.1161/strokeaha.115.011721