RESEARCH ARTICLE

Relationship Between Thrombolysis-to-Puncture Time and Outcomes of Endovascular Thrombectomy in Acute Ischemic Stroke

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Abstract

Background and Objectives

Intravenous thrombolysis (IVT) followed by endovascular thrombectomy (EVT) improves functional outcomes in patients with acute ischemic stroke (AIS) caused by large vessel occlusion (LVO). There are limited data on the effect of thrombolysis-to-puncture time (TTP) on outcomes in patients with AIS undergoing IVT plus EVT.

Methods

We selected 1,104 patients receiving IVT + EVT for anterior circulation LVO stroke from 2 prospective nationwide registries (259 cases from ANGEL-ACT in China: November 2017 to March 2019, 845 cases from German Stroke Registry-Endovascular Treatment in Germany: June 2015 to December 2019). Based on the TTP, eligible patients were divided into 4 groups (≤30 min, 31–50 min, 51–70 min, and >70 min). The radiologic and clinical outcomes (e.g., successful recanalization [modified Thrombolysis in Cerebral Infarction score of 2b–3] at final angiogram, modified Rankin Scale [mRS] score of 0–2 at 90 days, any intracranial hemorrhage [ICH], and symptomatic ICH within 24 hours) among the 4 groups were compared by χ^2 tests for trend and using multivariable logistic regression models.

Results

In the 4 groups from ≤30 min to >70 min, 226, 282, 230, and 366 patients were included, respectively. An increased TTP was associated with a lower chance of successful recanalization ($p = 0.016$) and mRS score 0–2 ($p = 0.002$). Compared with the group of ≤30 min, the group of >70 min was less likely to achieve successful recanalization (adjusted odds ratio [OR] = 0.47, 95% CI 0.25–0.89) and the groups of 50–70 min and >70 min had a reduced probability of mRS score 0–2 (adjusted OR = 0.50, 95% CI 0.33–0.78; adjusted OR = 0.56, 95% CI 0.37–0.85). No significant differences were found for any ICH or symptomatic ICH among the 4 groups after adjustment with potential confounders.

Discussion

Delay from thrombolysis to puncture should be minimized when considering bridging IVT before EVT for patients with AIS due to anterior circulation LVO. Further studies are warranted to verify and expand on these findings.

Trial Registration Information

ClinicalTrials.gov, NCT03370939 and NCT03356392.

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Introduction

Endovascular thrombectomy (EVT) has become the standard of care in select patients with acute ischemic stroke due to large vessel occlusions (AIS-LVOs) in the anterior circulation.[1] For AIS-LVO within 4.5 hours, intravenous thrombolysis (IVT) with alteplase before EVT remains the standard approach for eligible patients based on the clinical evidence in pivotal randomized controlled trials.[2] However, the fact that IVT has limited efficacy in proximal LVO raises the question whether EVT alone could be a viable alternative to the standard strategy of IVT plus EVT.[3] Recently, a meta-analysis of 6 randomized controlled trials suggested that EVT alone is highly unlikely to be noninferior to IVT plus EVT within 4.5 hours of symptom onset in patients with anterior circulation AIS-LVO when applying stringent non-inferiority margins.[4,5] Therefore, IVT as evidence-based therapy remains indicated before EVT in eligible patients. Current guidelines recommend that alteplase should be administered to all eligible patients before thrombectomy.[1] However, available data do not directly address the question of whether patients should be observed after intravenous alteplase administration to assess for clinical response before pursuing thrombectomy, so the impact of the time from IVT to EVT on outcome remains uncertain. On the one hand, the limited efficacy of IVT before EVT may be due to the relatively short duration of time from IVT administration to groin puncture that may have precluded the full therapeutic effect of IVT. It is assumed that most benefits would be amplified when the time gap between IVT and EVT is larger.[6-8] On the other hand, we can infer that because disability outcomes at 90 days are directly associated with time from symptom onset to groin puncture,[9] any cause for delay to thrombectomy, including observing for a clinical response after IVT, should be avoided.[1]

Therefore, in this study, we aimed to investigate the association of thrombolysis-to-puncture time (TTP) with clinical and radiographic outcomes in patients with AIS-LVO through a pooled analysis of 2 prospective nationwide registry databases.

Methods

Study Design and Population

We performed a post hoc, pooled analysis of the ANGEL-ACT (Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke) and German Stroke Registry-Endovascular Treatment (GSR-ET) registries. The ANGEL-ACT was a nationwide prospective registry of 1793 consecutive adult patients with AIS caused by LVO treated with EVT at 111 hospitals from 26 provinces between November 2017 and March 2019, aiming to reflect the current status of EVT in real-world clinical practice in China. The GSR-ET was established in June 2015 as an ongoing, prospective, nationwide registry of 25 university and community hospitals enrolling consecutive patients with AIS-LVO with the aim to evaluate outcome, safety, and process parameters of EVT in Germany. Details of the study design, inclusion/exclusion criteria, and data collection standards for the 2 registries have been reported previously.[10,11] The protocols were approved by the ethics committees of all centers, and all participants or their legal representatives provided written informed consent. The study procedures were in accordance with the 1964 Helsinki Declaration and its later amendments.

All centers participating in the 2 registry studies offered 7-day × 24-h thrombectomy. Each qualified center must conduct at least 20 neurothrombectomy procedures each year. Each interventional investigator must be experienced and have participated in at least 10 neurothrombectomy procedures overall. Not all centers performed perfusion imaging before thrombectomy. In some centers with good imaging resources and installed Rapid Processing of Perfusion and Diffusion software, when patients had a longer stroke-onset time (over 6 hours), perfusion imaging was performed to select patients suitable for thrombectomy. Alteplase was administered in the CT room or emergency department after completing CT ± CT angiography scans.

For the purpose of this analysis, we used the following inclusion criteria: (1) isolated intracranial LVO in the anterior circulation (i.e., internal carotid artery or middle cerebral artery M1/M2 segment) recommended by the guidelines for bridging thrombectomy,[1] (2) direct arrival at EVT centers (mothership), (3) IVT with alteplase (0.9 mg/kg) before EVT, (4) known time from thrombolysis to puncture, (5) baseline imaging with ASPECTS (Alberta Stroke Program Early CT Score) of 6–10, and (6) prestroke modified Rankin Scale (mRS) score of 0–2. Tandem lesions were not excluded because it was not necessary or even inappropriate to exclude tandem lesions when analyzing the relationship between the TTP and outcomes. The characteristics of tandem lesions had been analyzed and presented in previously published literature from both databases.[10,12] Finally, a total of 1,104 patients were eligible for this analysis. A detailed flowchart of patient selection is shown in Figure 1.

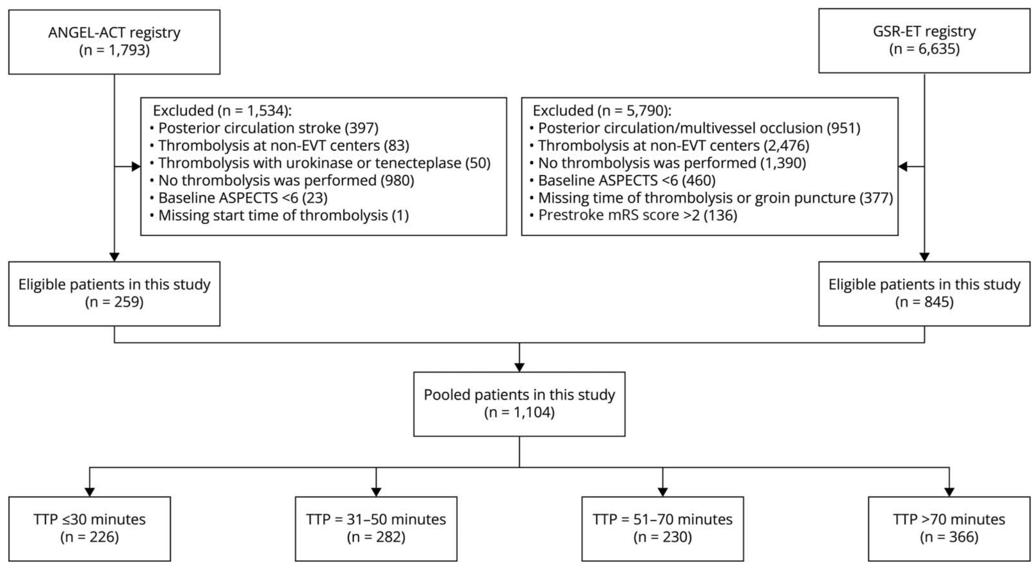
Study Outcome Measures

The outcome measures included successful recanalization at final angiogram, functional independence at 90 days, any intracranial hemorrhage (ICH), and symptomatic ICH within 24 hours. Successful recanalization was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b–3.[13] Functional independence was defined as a mRS score of 0–2 assessed by trained and independent investigators.[14] Any ICH was identified by follow-up imaging regardless of any clinical deterioration. Symptomatic ICH was evaluated using the Heidelberg Bleeding Classification.[15]

Statistical Analysis

All data were presented as frequency (percentage) for categorical variables. First, a univariable comparison of baseline

Figure 1 Flowchart of Patient Selection



ANGEL-ACT = Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke in China, ASPECTS = Alberta Stroke Program Early CT Score, EVT = endovascular thrombectomy, GSR-ET = German Stroke Registry-Endovascular Treatment, TTP = thrombolysis-to-puncture time.

and outcome variables between the 2 registries was conducted by the Pearson χ^2 test. Second, the pooled eligible patients were divided into 4 groups (≤30 min, 31–50 min, 51–70 min, and >70 min) according to TTP. The cutoff value of time increments was determined based on the interquartile range of TTP to be analyzed and considering its clinical significance. A univariable comparison of baseline characteristics and outcome measures among the 4 groups was performed using the Pearson χ^2 test and χ^2 test for trend, respectively. Last, the association of TTP with outcomes was explored using the multivariable logistic regression model with adjustment for potential confounders, including data origin (ANGEL-ACT or GSR-ET), sex, age, prestroke mRS score, NIH Stroke Scale (NIHSS) score, ASPECTS, occlusion site, and underlying intracranial atherosclerotic disease ([ICAD], defined as fixed stenosis degree >70% or >50% with distal blood flow impairment or evidence of repeated reocclusion). The selection of confounding factors was based on the following 2 points: (1) a priori on the basis of established associations and/or plausible biological relations with the outcomes of interest; (2) significant differences in the baseline characteristics among sites/groups. In addition, to improve the robustness and readability of the relationship between TTP and outcomes, trend plots were drawn using the generalized additive model.

Results

For this analysis, a total of 1,104 patients were enrolled in ANGEL-ACT (n = 259) and GSR-ET (n = 845). Baseline and outcome characteristics of patients from 2 registries are provided in eTable 1. There were significant differences in patient characteristics between both registries, except for ASPECTS before treatment, successful recanalization at final angiogram, and symptomatic ICH within 24 hours.

Univariable Between-Group Comparisons

The eligible patients were divided into 4 groups based on TTP, that is, less than or equal to 30 min (n = 226), 31–50 min (n = 282), 51–70 min (n = 230), and greater than 70 min (n = 366). Comparisons of patient characteristics among the 4 groups are provided in Table 1. As for the baseline, there were significant differences among them in data source, age, prestroke mRS score, and underlying ICAD and no significant differences were found in sex, NIHSS score, ASPECTS, and occlusion site. As for the outcome presented in Table 2, the χ^2 test for trend showed that from groups of ≤30 min to >70 min, the rate of successful recanalization at final angiogram and the proportion of mRS score 0–2 at 90 days had a significant downward trend while the risk of any ICH within 24 hours had a significant upward trend. The change trend of the odds of symptomatic ICH was not statistically significant.

Multivariable Analysis of Association Between TTP and Outcomes

Results of the multivariable logistic analyses are presented in Table 3. Compared with the group of ≤30 min, the group of >70 min was less likely to achieve successful recanalization at final angiogram (adjusted odds ratio [OR] = 0.47, 95% CI 0.25–0.89, p = 0.020) and the groups of 51–70 min and >70 min had a reduced probability of mRS score 0–2 at 90 days (adjusted OR = 0.50, 95% CI 0.33–0.78, p = 0.002; adjusted OR = 0.56, 95% CI 0.37–0.85, p = 0.006). No

Table 1 Baseline Characteristics Grouped by Thrombolysis-to-Puncture Time

Variable name	Thrombolysis-to-puncture time, min ≤30 (n = 226)	31–50 (n = 282)	51–70 (n = 230)	>70 (n = 366)	*p* Value
Data origin					<0.001[a]
ANGEL-ACT registry	25 (11.1)	42 (14.9)	40 (17.4)	152 (41.5)	
GSR-ET registry	201 (88.9)	240 (85.1)	190 (82.6)	214 (58.5)	
Sex					0.393[a]
Female	101 (44.7)	141 (50.0)	121 (52.6)	179 (48.9)	
Male	125 (55.3)	141 (50.0)	109 (47.4)	187 (51.1)	
Age, y					0.011[a]
≤40	12 (5.3)	7 (2.5)	2 (0.9)	11 (3.0)	
41–60	38 (16.9)	54 (19.1)	34 (14.8)	83 (22.7)	
61–80	115 (51.1)	138 (48.9)	132 (57.4)	198 (54.1)	
>80	60 (26.7)	83 (29.4)	62 (27.0)	74 (20.2)	
Prestroke mRS score					0.049[a]
0	194 (85.8)	228 (80.9)	188 (81.7)	322 (88.0)	
1–2	32 (14.2)	54 (19.1)	42 (18.3)	44 (12.0)	
NIHSS score					0.290[a]
≤5	20 (8.9)	22 (7.9)	11 (4.8)	30 (8.2)	
6–10	45 (20.0)	52 (18.6)	41 (17.9)	92 (25.1)	
11–15	65 (28.9)	84 (30.1)	77 (33.6)	100 (27.3)	
>15	95 (42.2)	121 (43.4)	100 (43.7)	144 (39.3)	
ASPECTS[b]					0.077[a]
6–8	73 (32.4)	76 (27.0)	73 (31.7)	134 (36.6)	
9–10	152 (67.6)	206 (73.0)	157 (68.3)	232 (63.4)	
Occlusion site					0.545[a]
Internal carotid artery	54 (23.9)	55 (19.5)	56 (24.3)	84 (23.0)	
Middle cerebral artery M1 segment	121 (53.5)	147 (52.1)	120 (52.2)	180 (49.2)	
Middle cerebral artery M2 segment	51 (22.6)	80 (28.4)	54 (23.5)	102 (27.9)	
Underlying ICAD[c]					<0.001[a]
Yes	7 (3.1)	8 (2.8)	7 (3.0)	38 (10.4)	
No	218 (96.5)	268 (95.0)	217 (94.3)	302 (82.5)	
Undetermined	1 (0.4)	6 (2.1)	6 (2.6)	26 (7.1)	

Abbreviations: ANGEL-ACT = Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke in China; ASPECTS = Alberta Stroke Program Early CT Score; GSR-ET = German Stroke Registry-Endovascular Treatment; ICAD = intracranial atherosclerotic disease; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.
Values are frequencies with percentages in parentheses, unless indicated otherwise.
[a] Calculated by the Pearson χ^2 test.
[b] Graded from 0 to 10, with 1 point subtracted from 10 for any evidence of early ischemic changes in each defined region on noncontrast CT or diffusion-weighted imaging.
[c] Defined as fixed stenosis degree >70% or >50% with distal blood flow impairment or evidence of repeated reocclusion.

significant differences were found for any ICH or symptomatic ICH within 24 hours among the 4 groups after adjustment with potential confounders. In addition, trend plots of outcomes with TTP were drawn using generalized additive models with adjustment for the same confounders as the logistic analysis (Figure 2). Among patients included in this

Table 2 Outcome Measures Grouped by Thrombolysis-to-Puncture Time

Variable name	Thrombolysis-to-puncture time, min				*p* Value
	≤30 (n = 226)	31–50 (n = 282)	51–70 (n = 230)	>70 (n = 366)	
Successful recanalization at final angiogram[a]					0.016[b]
Yes	210 (93.3)	249 (89.9)	209 (92.1)	317 (86.6)	
No	15 (6.7)	28 (10.1)	18 (7.9)	49 (13.4)	
mRS score 0–2 at 90 d					0.002[b]
Yes	129 (62.3)	142 (55.3)	92 (44.2)	165 (49.7)	
No	78 (37.7)	115 (44.7)	116 (55.8)	167 (50.3)	
Any ICH within 24 h					<0.001[b]
Yes	10 (4.4)	17 (6.0)	14 (6.1)	48 (13.4)	
No	215 (95.6)	264 (94.0)	214 (93.9)	309 (86.6)	
Symptomatic ICH within 24 h[c]					0.128[b]
Yes	1 (0.4)	2 (0.7)	3 (1.3)	6 (1.7)	
No	223 (99.6)	277 (99.3)	225 (98.7)	351 (98.3)	

Abbreviations: ANGEL-ACT = Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke in China; GSR-ET = German Stroke Registry-Endovascular Treatment; ICH = intracranial hemorrhage; mRS = modified Rankin Scale; mTICI = modified Thrombolysis in Cerebral Infarction; NIHSS = NIH Stroke Scale.
Values are frequencies with percentages in parentheses, unless indicated otherwise.
[a] Defined as mTICI score 2b–3.
[b] Calculated by the χ^2 test for trend.
[c] According to the Heidelberg Bleeding Classification.

analysis, 671 received general anesthesia. When the type of anesthesia (general anesthesia vs not) was added as a confounder to the multivariable regression equation for analysis, we found that there was no substantial change in the correlation and strength between TTP and various outcomes (eTable 2).

Discussion

Our study included large data sets of patients treated with IVT and EVT contributed by 136 centers in China and Germany over 3–8 years of routine clinical practice after 2015 when EVT became evidence-based first-line treatment for AIS-LVO. This pooled analysis of 2 prospective nationwide registries in China and Germany examined the association of TTP with outcomes after EVT in patients with AIS-LVO of anterior circulation and found that a shortened TTP interval (≤30 min) was associated with a higher rate of successful recanalization and 90-day functional independence while the correlation between TTP and ICH was not observed.

The therapeutic effect of pretreatment with IVT in patients with LVO eligible for EVT is unsatisfactory, only resulting in successful recanalization in 1 of 10 cases before EVT.[16] Moreover, tandem occlusions or internal carotid artery occlusions (T/L-type) seem to be the least responsive to IVT pretreatment, and successful recanalization can hardly be achieved by IVT alone.[17] By contrast, the successful recanalization rate for LVO treated with EVT is as high as 80%–90%,[18-20] so shortening the TTP could theoretically reduce the time to target vessel recanalization. When considering bridging therapy, it is more important to shorten the delay from thrombolysis to puncture than to wait for the full effect of thrombolytic agents.[1] In an individual patient data meta-analysis of 5 randomized clinical trials of patients with AIS-LVO, earlier treatment with EVT compared with medical therapy alone was associated with lower chance of disability at 90 days[9] The time from stroke onset to groin puncture for EVT has the greatest benefit within 2 hours while the benefit becomes insignificant after 7.3 hours, emphasizing the importance of enhancing patient awareness and prehospital and in-hospital management to shorten onset-to-treatment time.[9] Notably, in-hospital processes of care are directly associated with improved functional outcome. For every 1,000 patients who received EVT and successfully achieved recanalization, it is estimated that 39 patients will have a lower degree of disability for every 15 minutes of shortening the time from door to puncture, including 25 patients who can achieve functional independence (mRS score 0–2) at 90 days.[9] In addition to faster door-to-puncture time, faster imaging-to-puncture time was associated with better 90-day functional outcomes,[9] but detailed information about the relationship between the TTP and outcomes was not available.

Table 3 Association of Thrombolysis-to-Puncture Time With Outcomes by Multivariable Logistic Analysis

Exposure variable[a]	Outcome variable: Successful recanalization at final angiogram[b] (n = 1,088)	mRS score 0–2 at 90 d (n = 997)	Any ICH within 24 h (n = 1,084)	Symptomatic ICH within 24 h[c] (n = 1,083)
Data origin				
ANGEL-ACT registry	Reference	Reference	Reference	Reference
GSR-ET registry	0.88 (0.49–1.57), 0.666	1.79 (1.20–2.65), 0.004	0.07 (0.04–0.12), <0.001	0.32 (0.08–1.27), 0.106
Sex				
Female	Reference	Reference	Reference	Reference
Male	1.58 (1.03–2.43), 0.036	0.93 (0.70–1.24), 0.627	0.69 (0.41–1.16), 0.165	0.81 (0.22–3.03), 0.758
Age, y				
≤40	Reference	Reference	Reference	Reference
41–60	2.18 (0.73–6.53), 0.165	0.49 (0.17–1.44), 0.196	0.52 (0.14–1.94), 0.332	—[b]
61–80	2.13 (0.76–5.97), 0.150	0.22 (0.08–0.63), 0.005	0.89 (0.26–2.99), 0.846	—[b]
>80	2.01 (0.67–5.97), 0.211	0.11 (0.04–0.33), <0.001	0.77 (0.20–2.99), 0.707	—[b]
Prestroke mRS score				
0	Reference	Reference	Reference	Reference
1–2	1.68 (0.87–3.24), 0.120	0.46 (0.31–0.70), <0.001	0.79 (0.34–1.85), 0.594	2.30 (0.61–8.72), 0.219
NIHSS score				
≤5	Reference	Reference	Reference	Reference
6–10	0.67 (0.24–1.87), 0.439	0.65 (0.33–1.27), 0.204	4.29 (0.52–35.34), 0.176	—[b]
11–15	0.69 (0.25–1.91), 0.476	0.38 (0.20–0.73), 0.004	4.05 (0.51–32.50), 0.188	—[b]
>15	0.47 (0.18–1.28), 0.140	0.20 (0.10–0.38), <0.001	6.76 (0.86–52.95), 0.069	—[b]
ASPECTS[d]				
6–8	Reference	Reference	Reference	Reference
9–10	1.47 (0.97–2.24), 0.072	1.39 (1.03–1.89), 0.032	0.90 (0.54–1.52), 0.704	0.36 (0.11–1.23), 0.103
Occlusion site				
Internal carotid artery	Reference	Reference	Reference	Reference
Middle cerebral artery M1 segment	1.26 (0.77–2.09), 0.361	1.42 (0.99–3.03), 0.054	0.62 (0.35–1.11), 0.107	0.79 (0.20–3.13), 0.740
Middle cerebral artery M2 segment	0.88 (0.49–1.56), 0.662	1.46 (0.95–2.24), 0.083	0.87 (0.42–1.80), 0.700	1.52 (0.30–7.73), 0.612
Underlying ICAD[e]				
Yes	Reference	Reference	Reference	Reference
No	0.60 (0.19–1.88), 0.378	1.16 (0.59–2.26), 0.672	1.77 (0.79–4.00), 0.167	—[f]
Undetermined	0.31 (0.08–1.18), 0.087	1.77 (0.69–4.55), 0.237	1.00 (0.32–3.09), 0.999	—[f]
Thrombolysis-to-puncture time, min				
≤30	Reference	Reference	Reference	Reference
31–50	0.61 (0.32–1.20), 0.151	0.79 (0.52–1.21), 0.280	1.40 (0.56–3.49), 0.467	1.45 (0.13–16.73), 0.767
51–70	0.83 (0.40–1.71), 0.614	0.50 (0.33–0.78), 0.002	1.10 (0.42–2.85), 0.846	2.53 (0.25–25.64), 0.433

Continued

Table 3 Association of Thrombolysis-to-Puncture Time With Outcomes by Multivariable Logistic Analysis *(continued)*

Exposure variable[a]	Outcome variable: Successful recanalization at final angiogram[b] (n = 1,088)	mRS score 0–2 at 90 d (n = 997)	Any ICH within 24 h (n = 1,084)	Symptomatic ICH within 24 h[c] (n = 1,083)
>70	0.47 (0.25–0.89), 0.020	0.56 (0.37–0.85), 0.006	1.77 (0.76–4.11), 0.182	3.03 (0.32–28.62), 0.333

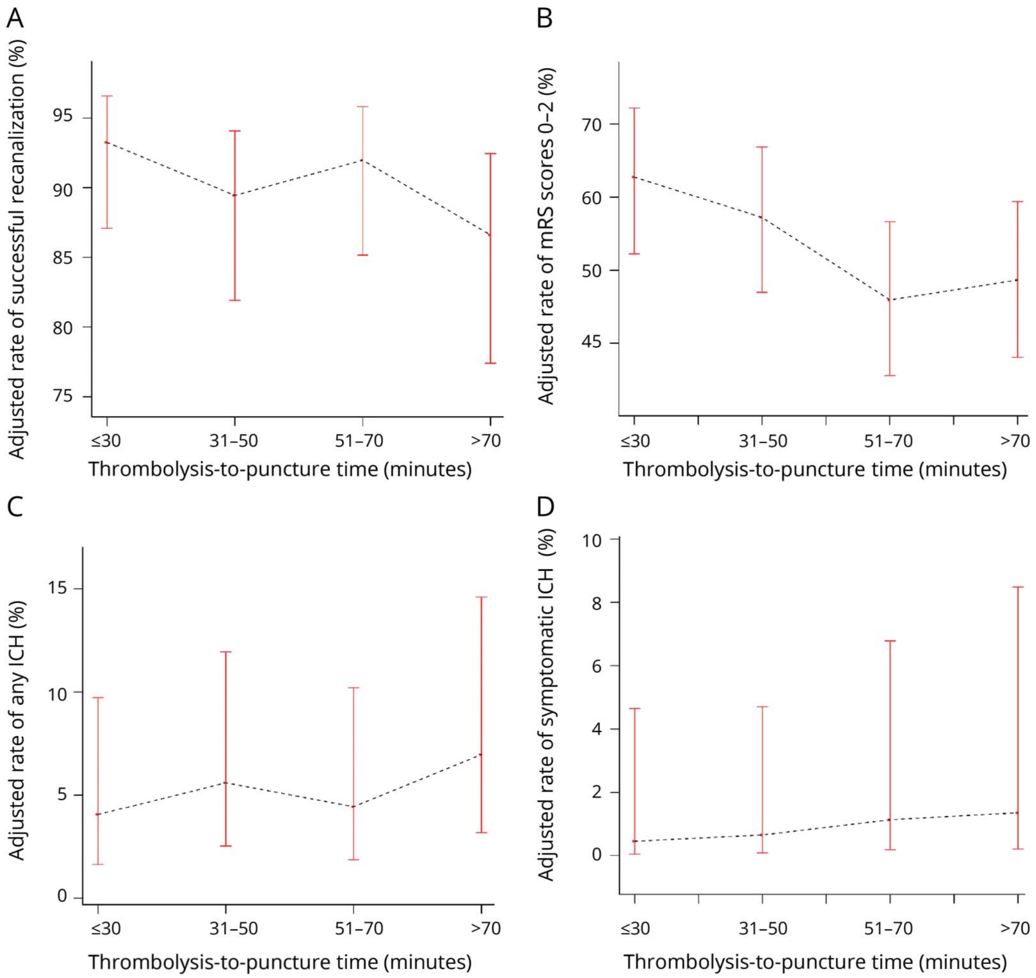
Abbreviations: ANGEL-ACT = Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke in China; ASPECTS = Alberta Stroke Program Early CT Score; GSR-ET = German Stroke Registry-Endovascular Treatment; ICAD = intracranial atherosclerotic disease; ICH = intracranial hemorrhage; mRS = modified Rankin Scale; mTICI = modified Thrombolysis in Cerebral Infarction; NIHSS = NIH Stroke Scale.
Values are adjusted odds ratios with 95% CIs in parentheses and *p* values.
[a] All exposure variables were included as covariates in multivariable models for adjustment.
[b] Defined as mTICI score 2b–3.
[c] According to the Heidelberg Bleeding Classification.
[d] Graded from 0 to 10, with 1 point subtracted from 10 for any evidence of early ischemic changes in each defined region on noncontrast CT or diffusion-weighted imaging.
[e] Defined as fixed stenosis degree >70% or >50% with distal blood flow impairment or evidence of repeated reocclusion.
[f] The model failed because of no events in the reference group.

Similar to our findings, a prospective cohort study in France demonstrated that, in patients who received bridging therapy (treated with IVT and indication of EVT), shortened delay between thrombolysis and puncture is associated with better functional outcome and a higher reperfusion rate, whereas delay is associated with higher risks of parenchymal hematoma and symptomatic ICH. However, they involved predominantly the "drip-and-ship" patients (66.4%) with early thrombolysis at the closest primary stroke centers before transportation to the thrombectomy centers and did not have the statistical power to estimate the effects of TTP on outcomes in "mothership" patients with primary stroke center bypass and direct transport to the thrombectomy centers.[21] This study, focusing on the mothership patients, was a different/unique perspective to previous studies on this topic, suggesting that the shorter the TTP, the better the patient's outcome would be, and thus using real-world data to support the 2019 guideline recommendation: any cause for delay to EVT, including observing for a clinical response after IVT, should be avoided.[1]

Based on the 2019 American Heart Association/ASA guideline for the early management of patients with AIS, it may be reasonable to choose tenecteplase (single IV bolus of 0.25 mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy (class of recommendation: IIb).[1] In this study, we included patients receiving alteplase before treatment; the findings of this analysis may not be valid for patients eligible for other intravenous thrombolytic agents (e.g., tenecteplase). For example, the Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial tenecteplase trial suggested that pretreatment with tenecteplase may be more effective than with alteplase regarding successful reperfusion before thrombectomy and improved clinical outcomes at 90 days.[22] Moreover, tenecteplase administration is a single bolus injection, unlike tPA, which may require a waiting time of 1-hour thrombolytic process when considering bridging therapy, thus greatly reducing the time delay between thrombolysis and puncture.

Some limitations of our study should be considered, warranting caution in the interpretation of our findings. First, because of the legal and regulatory restrictions on the security of data use across countries, we had to convert the continuous variables (age, TTP) and discrete variables (NIHSS score, ASPECTS) in both databases into categorical variables for statistical analysis, which might, therefore, have caused a degree of information loss and test power decrease. Second, the observational design may imply some degree of confounding by patient selection biases and residual baseline differences, despite efforts to mitigate them. Third, perceptual and technical differences between centers are a possibility that could have affected the assessment of mTICI score and ICH classification, which were self-reported by local investigators in all of the GSR-ET registry and a small part of the ANGEL-ACT registry. Thus, no central adjudication of imaging may introduce rater bias,[23] although all raters were trained by committee-assigned imaging specialists before initiating patient enrollment. Fourth, some selection bias may be present due to the nearly 5% rate of missing time from thrombolysis to puncture and the nearly 10% rate of missing 90-day outcome data, handled by case-wise deletion. Fifth, the patients who achieved recanalization/recovery after IVT and did not undergo thrombectomy (particularly in the group that took longer to initiate arterial puncture after IVT) were not included in this analysis because their data were not systematically recorded in the registries, thereby underestimating the full therapeutic effect of IVT. Sixth, we must recognize that there are huge differences between China and Germany in the health care system and income economy, so it is of great significance to identify the gaps between the 2 countries in prehospital and in-hospital workflow, reimbursement policies for EVT devices and other treatment costs, and the proportion of rehabilitation training after discharge. Unfortunately, the abovementioned variables have not been

Figure 2 Trend Plots of Outcomes With Thrombolysis-to-Puncture Time Were Drawn Using Generalized Additive Models With Adjustment for Data Origin, Sex, Age, Prestroke mRS Score, NIHSS Score, ASPECTS, Occlusion Site, and Underlying ICAD



Successful recanalization was defined as mTICI score 2b–3. Symptomatic ICH was identified according to the Heidelberg Bleeding Classification. ASPECTS = Alberta Stroke Program Early CT Score, ICAD = intracranial atherosclerotic disease, ICH = intracranial hemorrhage, mRS = modified Rankin Scale, mTICI = modified Thrombolysis in Cerebral Infarction, NIHSS = NIH Stroke Scale.

fully collected, making it impossible to analyze and compare them. Finally, we did not have data available regarding percutaneous puncture approach, specifically transfemoral vs transradial access; however, transradial thrombectomy is not the most common method.[24] Currently, it is believed that transradial thrombectomy is a safe alternative to transfemoral thrombectomy in patients with LVO-AIS, and transradial and transfemoral thrombectomy resulted in similar clinical outcomes.[24,25] Further studies on the optimal approach are necessary based on patient and disease characteristics. Unfortunately, our 2 databases were not preset to collect information on transradial access treatment, so we cannot know the proportion of transradial treatment and its impact on the results of this study, although this impact is likely to be insignificant.

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Author Contributions

X. Tong: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. B. Jia: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. G. Ma: major role in the acquisition of data. X. Zhang: major role in the acquisition of data. J. Fiehler: major role in the acquisition of data. F. Flottmann: major role in the acquisition of data. M Bechstein: major role in the acquisition of data. G. Broocks: major role in the acquisition of data. U. Hanning: major role in the acquisition of data. H.C. Kniep: major role in the acquisition of data. G. Thomalla: major role in the acquisition of data. M. Deb-Chatterji: major role in the acquisition of data. Gerhard Schön: analysis or interpretation of data. Y. Zhang: analysis or interpretation of data. F Gao: major role in the acquisition of data. N. Ma: major role in the acquisition of data. D. Mo: major role in the acquisition of data. Z. Miao: study concept or design; analysis or interpretation of

TAKE-HOME POINTS

→ In this pooled analysis of 2 nationwide registries, we found that shortening the time delay from IVT administration to groin puncture (start of EVT) was associated with a higher rate of successful recanalization and a better chance of 90-day functional independence.

→ Our results, despite the stated limitations, support current guidelines to avoid EVT delay caused by observing for a clinical response after IVT if they are being planned for bridging therapy.

→ Meanwhile, these results emphasize that within the time window of bridging therapy, time lapse equals brain damage.

→ Therefore, our findings provide a basis for further trials to determine whether the functional outcome of patients with stroke can be significantly improved by optimizing the time from thrombolysis to thrombectomy.

data. L. Meyer: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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