Prospective Cohort Study

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Bridging therapy versus direct endovascular thrombectomy in patients with established large infarct: a prospective cohort study

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Background: Whether patients with large core infarctions should undergo intravenous thrombolysis (IVT) before endovascular thrombectomy (EVT) is currently a subject of controversy. The study aimed to investigate the association of prior use of IVT with outcomes of EVT patients with large core infarctions.

Materials and methods: This prospective cohort included patients with acute large vessel occlusion and Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of 0-5 from 38 stroke centers across China between November 2021 and February 2023. The primary outcome was defined as favorable functional outcomes, which is 90-day modified Rankin Scale (mRS) scores ranging from 0 to 3. Procedural outcomes included measures of successful and effective recanalization. Safety outcomes included the incidence of any intracranial hemorrhage (ICH), symptomatic ICH, and 90-day mortality.

Results: Of 490 patients, 122 (24.5%) were treated with IVT before EVT. Bridging therapy and its transfer modes showed no association with any of the measured outcomes. Compared to direct EVT, bridging therapy was associated with a decreased risk of symptomatic ICH in very elderly patients and a decreased risk of any ICH in patients with admission NIHSS scores of 20 or higher. Additionally, early stroke severity may alter the odds of any ICH in patients with bridging therapy versus direct EVT (inverse probability weighting adjusted *P* value for interaction = 0.003 and 0.007, respectively).

Conclusion: In large core infarction patients with high admission NIHSS or very elderly age, bridging therapy appears to have some advantages over direct EVT in reducing the risk of ICH.

Keywords: clinical outcomes, endovascular thrombectomy, intravenous thrombolysis, ischemic stroke, large core infarctions

Introduction

From 2015 to 2018, seven landmark randomized controlled trials (RCTs) provided compelling evidence for the efficacy of endovascular thrombectomy (EVT), thereby establishing EVT as the mainstream treatment for acute ischemic stroke (AIS) with large vessel occlusion (LVO)[1–8]. With the progression of thrombectomy techniques and relentless exploration, four recent trials supplied further cogent results for the effectiveness of EVT in patients with large core infarctions [Alberta Stroke Program Early Computed Tomography Score (ASPECTS) $\leq$ 5][9–12], which were not included in early investigations, due to their limited redeemable tissue and significantly increased risk of intracranial hemorrhage (ICH)[13].

The utility of intravenous thrombolysis (IVT) before EVT is currently a subject of controversy. As the traditional standard treatment for the hyperacute phase of ischemic stroke, IVT remains extensively administered to most eligible patients, even after mechanical thrombectomy has been proven efficacious. One

HIGHLIGHTS

- Bridging IVT was not associated with the overall likelihood of 90-day favorable outcomes, successful reperfusion, effective recanalization, any ICH, symptomatic ICH, and 90-day mortality.
- Regardless of whether direct EVT was performed within 4.5 h, bridging therapy was associated with a decreased risk of symptomatic ICH in very elderly patients and a decreased risk of any ICH in patients with severe symptoms.
- The severity of the stroke influenced the relationship between prior use of IVT and the risk of any ICH.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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International Journal of Surgery (2025) 111:520–528

Received 10 April 2024; Accepted 25 July 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery.

Published online 14 August 2024

http://dx.doi.org/10.1097/JS9.0000000000002017

argument posits that IVT can increase early reperfusion, dissolve residual distal thrombi after EVT, enhance perfusion to the brain's remote territories, reduce the number of required EVT passes, and decrease the occurrence of both impaired microvascular reperfusion and microvascular thrombosis[14–18]. Conversely, another concern is that IVT may increase the risk of ICH and potentially lead to thrombus fragmentation, which could result in suboptimal reperfusion of distal cerebral tissue and the loss of the optimal window for EVT[19,20]. Existing trials indicated that the effect of EVT was not influenced by prior IVT[21–26], and no real benefit of IVT was observed in the subgroup analyses from recently published trials for patients with large core infarction[9–11], raising the question about the necessity of IVT treatment before EVT.

Previous research was contentious regarding whether patients with large core infarctions should undergo bridging thrombolysis followed by thrombectomy or proceed directly to thrombectomy. Particularly, there is still a scarcity of evidence concerning large core infarctions. Understanding the benefits and safety of combining IVT with EVT versus direct EVT, especially in patients with large ischemic cores, is crucial for optimizing recanalization and reperfusion strategies in the management of AIS. Additionally, research focusing on patients with large core infarctions in China is particularly valuable because China experiences a large number of strokes occurring outside the treatment window period, and the duration of ischemia is positively correlated with infarct core volume[27]. Research focusing on patients with large core infarctions in China is particularly valuable. Thus, we aimed to investigate the association between IVT use and functional, procedural, and safety outcomes of EVT patients with large core infarctions, and further explore the heterogeneous effect across specific subgroups of patients who might benefit from personalized reperfusion plans.

Materials and methods

Study design

The data of this study was obtained from a prospective, multicenter cohort study of early treatment in acute stroke. The prospective, observational, and nationwide registry is ongoing, including patients with acute LVO from 38 stroke centers across 12 provinces of China, with data collection spanning from 1 November 2021, to 8 February 2023 (URL: http://www.chictr.org.cn; Unique identifier: ChiCTR2100051664). Each center included in this study must meet the following criteria: performing more than 50 mechanical thrombectomies annually, and each neurointerventionist must complete at least 10 thrombectomies per year. EVT included stent retrievers, aspiration, balloon angioplasty, stenting, intra-arterial thrombolysis, mechanical fragmentation, or any combination of these approaches. The standardization of EVT procedures was described in the supplementary materials (eMethods section, Supplemental Digital Content 2, http://links.lww.com/JS9/D333). The decision to perform EVT was left to the discretion of the local physicians. The study protocol was approved by the ethics committees of the Second Affiliated Hospital of the Army Medical University participating hospitals. All enrolled patients or their legally authorized representatives provided written informed consent before enrollment. Since this study is observational and will not affect the treatment of patients, informed consent can be obtained after the patient's condition has relatively stabilized. This work has been reported in line with the STROCSS criteria[28], Supplemental Digital Content 1, http://links.lww.com/JS9/D332.

Inclusion and exclusion criteria

The inclusion criteria for this study were as follows: (1) age older than or equal to 18; (2) AIS due to anterior circulation LVO, defined as occlusion of the internal carotid artery (ICA) or the M1 segment or M2 segment of the middle cerebral artery (MCA); (3) large ischemic core on NCCT (defined as an ASPECTS of 0–5); (4) symptom presentation within 24 h (if the exact presentation time was unavailable, 'time last known well' within 24 h was used as a reference). The exclusion criteria were as follows: (1) pre-stroke modified Rankin Score (mRS) greater than 2; (2) uncompleted the 90-day follow-up; and (3) serious or terminal illness. The study flow chart is shown in Supplementary Figure 1, Supplemental Digital Content 2, http://links.lww.com/JS9/D333.

Data collection

Patients' demographic factors, vascular risk factors, clinical assessments, IVT use, routing paradigm, and outcomes were obtained from the MAGIC registry[29]. IVT was administered according to the current guidelines within 4.5 h from symptom onset at the first hospital (alteplase 0.9 mg/kg, maximum 90 mg, over 1 h with 10% initial bolus). The admission modes of patients were also recorded, including "drip-and-ship" (received IVT treatment in a primary stroke center and EVT in a comprehensive stroke center), and "mothership" (received both IVT and EVT in comprehensive stroke centers)[30]. Stroke severity was assessed by well-trained doctors using the National Institutes of Health Stroke Scale (NIHSS) score on admission, before the initiation of reperfusion therapy. Baseline imaging, including digital subtraction angiograms (DSA), CT angiography (CTA), NCCT, and MRI were reviewed by local investigators at each participating center. The baseline ASPECTS was used to assess the extent of infarct hypoattenuation on pre-treatment NCCT or MRI. The stroke etiology was classified according to Trial of Org10172 in Acute Stroke Treatment (TOAST). The occlusion site was classified into 3 categories, including ICA, the M1 segment, or the M2 segment of the MCA. Collateral flow was defined according to the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) scale. Good collaterals were defined as ASITN/SIR scores 3–4, and poor collaterals were defined as ASITN/SIR scores 0–2.

Outcomes

The primary outcomes were favorable functional outcomes, defined as mRS scores of 0–3 at 90 days, reflecting a range from no symptoms to moderate disability while still being able to walk independently, following previous studies on anterior circulation stroke with low baseline ASPECTS[9–11,31–33]. The mRS scores were recorded during a follow-up visit or telephone encounter 90 days after the stroke by local physicians or registered nurses. Secondary outcomes consisted of successful reperfusion and effective recanalization. Successful reperfusion was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b or 3 on the final angiographic series. Effective recanalization was defined as LVO patients achieving successful reperfusion after EVT with functional independence (mRS 0–2) at 90 days. Safety outcomes included any ICH, symptomatic ICH, and 90-day mortality. Symptomatic ICH was defined as evidence of any ICH and a neurological worsening greater than or equal to 4 points on the NIHSS within 48 h after reperfusion treatment, according to the Heidelberg Bleeding Classification[34]. Patients' demographic factors, vascular risk factors, clinical assessments, IVT use, routing paradigm, and outcomes were each evaluated by different researchers and finally summarized by an additional researcher. The researcher evaluating the outcomes was blinded to the other patients' data.

Statistical analysis

The general characteristics of the main study population and sensitivity analysis sample were expressed as percentages for categorical variables and as medians (interquartile range, IQR) for continuous variables. Patients were divided into two groups according to whether IVT was used before EVT. Baseline characteristics were compared between the treatment groups, and the magnitude of between-group differences was assessed by calculating the absolute standardized difference (ASD). The *P* values in Table 1 were calculated by Mann–Whitney U tests for continuous variables and χ^2 tests for categorical variables.

In the main analysis, two models were employed to estimate the impact of prior IVT use and admission modes on outcomes. Model 1 was an unweighted multivariable logistic regression, adjusted for the following covariates: age, sex, admission NIHSS, ASPECTS, current smoking, atrial fibrillation, diabetes, hypertension, hyperlipidemia, infarcted hemisphere, TOAST etiology, occlusion site, time from onset to puncture ($\leq$ 6h or $>$ 6h), and collateral flow. Model 2 was an inverse probability weighting (IPW) adjusted logistic regression, where propensity scoring was used to weight patients by the inverse probability of treatment using stabilized inverse weights. The propensity score was estimated using a non-parsimonious multivariable logistic regression model with the treatment group as the dependent variable and including all the covariates listed in Model 1. The effects of IVT on outcomes in each subgroup were calculated by IPW-weighted logistic regression models, and the effect modification by covariates was evaluated on multiplicative scales including interaction terms in the IPW-weighted logistic regression model, and statistical significance was evaluated by Wald test.

Two-sided *P* values less than 0.05 and 95% CIs for the odds ratio (OR) that excluded 1.0 were considered statistically significant. All statistical analyses were performed using R (R Foundation for Statistical Computing), version 4.3.1. There was no missing data on interventions, selected covariates, and outcomes.

Table 1

Comparison of baseline characteristics by IVT Use before EVT in the main study population and sensitivity analysis sample.

	Main study population				Sensitivity analysis			
	Direct EVT (*n* = 368)	Bridging therapy (*n* = 122)	ASD (%)	*P*	Direct EVT (*n* = 109)	Bridging therapy (*n* = 122)	ASD (%)	*P*
Age, years	69 (58–78)	69 (61–77)	10.3	0.472	72 (62–80)	69 (61–77)	9.8	0.283
Female, *n* (%)	159 (43.2)	50 (41.0)	4.5	0.667	60 (55.0)	50 (41.0)	28.4	0.033
Baseline NIHSS	17 (14–21)	17 (14–20)	7.2	0.627	18 (14–22)	17 (14–20)	8.4	0.465
Baseline ASPECTS	4 (2–5)	4 (2–5)	12.4	0.094	4 (2–5)	4 (2–5)	7.5	0.321
Smoking, *n* (%)	123 (33.4)	28 (23.0)	23.4	0.030	27 (24.8)	28 (23.0)	4.3	0.746
Atrial fibrillation, *n* (%)	170 (46.2)	51 (41.8)	8.9	0.398	59 (54.1)	51 (41.8)	24.9	0.061
Diabetes, *n* (%)	50 (13.6)	23 (18.9)	14.3	0.157	13 (11.9)	23 (18.9)	19.3	0.147
Hypertension, *n* (%)	222 (60.3)	75 (61.5)	2.4	0.822	72 (66.1)	75 (61.5)	9.5	0.470
Hyperlipidemia, *n* (%)	84 (22.8)	22 (18.0)	11.9	0.265	30 (27.5)	22 (18.0)	22.8	0.085
Right hemisphere, *n* (%)	182 (49.5)	60 (49.2)	0.6	0.958	62 (56.9)	60 (49.2)	15.5	0.242
TOAST etiology, *n* (%)			20.6	0.135			31.0	0.068
LAA	101 (27.4)	45 (36.9)			25 (22.9)	45 (36.9)		
CE	216 (58.7)	61 (50.0)			68 (62.4)	61 (50.0)		
Others	51 (13.9)	16 (13.1)			16 (14.7)	16 (13.1)		
Occlusion location, *n* (%)			26.6	0.041			46.8	0.003
ICA	166 (45.1)	40 (32.8)			60 (55.0)	40 (32.8)		
M1 segment	168 (45.7)	65 (53.3)			41 (37.6)	65 (53.3)		
M2 segment	34 (9.2)	17 (13.9)			8 (7.3)	17 (13.9)		
Onset to puncture $\leq$ 6h, n (%)	178 (48.4)	62 (50.8)	4.9	0.639	NA	62 (50.8)	NA	NA
ASITN/SIR 3-4, *n* (%)	55 (14.9)	27 (22.1)	18.6	0.065	9 (8.3)	27 (22.1)	39.4	0.004
90-day mRS 0–3, *n* (%)	137 (37.2)	44 (36.1)	2.4	0.818	39 (35.8)	44 (36.1)	0.6	0.964
Successful reperfusion, *n* (%)	316 (85.9)	107 (87.7)	5.4	0.609	98 (89.9)	107 (87.7)	7.0	0.597
Effective recanalization, *n* (%)	75 (20.4)	27 (22.1)	4.3	0.680	22 (20.2)	27 (22.1)	4.8	0.718
Any ICH, *n* (%)	136 (37.0)	44 (36.1)	1.9	0.860	36 (33.0)	44 (36.1)	6.4	0.628
Symptomatic ICH, *n* (%)	53 (14.4)	12 (9.8)	14.0	0.198	10 (9.2)	12 (9.8)	2.3	0.864
90-day mortality, *n* (%)	154 (41.8)	51 (41.8)	0.1	0.993	52 (47.7)	51 (41.8)	11.9	0.368

All continuous variables were presented median (interquartile range, IQR).

ASD, absolute standardized difference; ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CE, cardioembolic; EVT, endovascular thrombectomy; ICA, internal carotid artery; ICH, intracranial hemorrhage; IQR, interquartile range; IVT, intravenous thrombolysis; LAA, large-artery atherosclerosis; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org10172 in Acute Stroke Treatment.

Results

Patient characteristics

Ultimately, a total of 745 anterior circulation large vessel ischemic stroke patients who met the inclusion criteria were enrolled in the study from November 2021 to February 2023. Additionally, 490 patients who underwent EVT, with or without IVT, and had a pre-treatment ASPECTS of 0–5 on non-contrast NCCT or MRI, were selected from this database as the main study population, as shown in Supplementary Figure 1, Supplemental Digital Content 2, http://links.lww.com/JS9/D333. The median (IQR) age of patients was 69 (59–78), and 209 patients (42.7%) were female. Of the 490 patients, 368 were in the direct EVT group, and 122 were in the bridging therapy group. The demographic data and baseline characteristics of the 2 groups are presented in Table 1.

Primary outcomes

Figure 1 and Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/D333 depicted the distribution of the 90-day mRS scores according to prior IVT use and admission modes in both the overall study population and the sensitivity analysis sample. The proportion of patients who achieved favorable functional outcomes at 90 days after stroke onset was similar between the direct EVT group and the bridging therapy group (37.2% vs. 36.1%, $P = 0.818$). After adjusting for the selected covariates, no significant differences were found in the chance of 90-day favorable outcomes between the bridging therapy and direct EVT groups, the drip-and-ship and direct EVT groups, the mothership and direct EVT groups, and the drip-and-ship and mothership groups (Fig. 2). Additionally, IVT showed no association with 90-day favorable outcomes across all subgroups, and no covariates significantly affected its effect size (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JS9/D333).

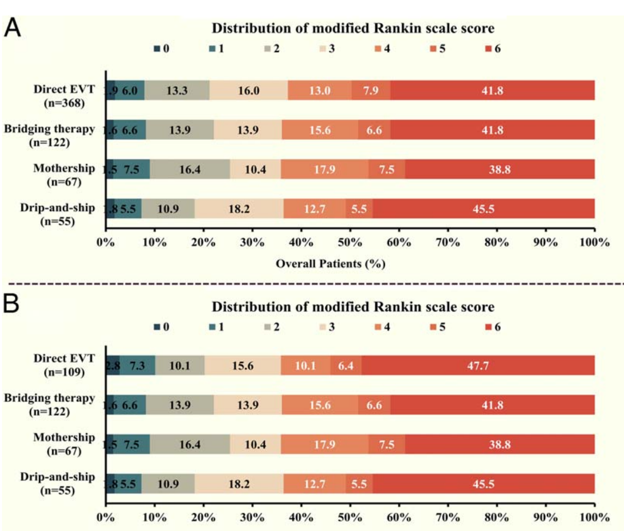

Figure 1. Distribution of the modified Rankin Scale score at 90 days According to Intravenous Thrombolysis Use before Endovascular Thrombectomy and Admission Modes. (A) The Overall study population; (B) Sensitivity analysis sample. Scores on the modified Rankin Scale range from 0 to 6, with 0 indicating no symptoms; 1, symptoms without clinical disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death.

Secondary outcomes

The chances of achieving successful reperfusion (87.7% vs. 85.9%, $P = 0.609$) and effective recanalization (22.1% vs. 20.4%, $P = 0.680$) were similar between bridging therapy and direct EVT groups. Adjusting for selected covariates, the odds of successful reperfusion and effective recanalization did not differ significantly between the bridging therapy and direct EVT group, the 'drip-and-ship' and direct EVT group, the 'mothership' and direct EVT group, or between the 'drip-and-ship' and 'mothership' group (Fig. 2).

The subgroup analyses (Supplementary Tables 3, 4, Supplemental Digital Content 2, http://links.lww.com/JS9/D333) revealed that the administration of IVT before EVT was associated with a reduced likelihood of achieving effective recanalization among very elderly thrombectomy patients (aged ≥ 80 years, IPW-adjusted OR = 0.855, [95% CI, 0.741–0.987]), and good collaterals thrombectomy patients (IPW-adjusted OR = 0.844, [95% CI, 0.718–0.993]). However, the potential modifying effects of age and ASITN/SIR score on the relationship between IVT and effective recanalization did not reach statistical significance, with IPW-adjusted P values for interaction being 0.105 and 0.225, respectively.

Safety outcomes

The risk of any ICH (37.0% vs. 36.1%, $P = 0.860$) and 90-day mortality (41.8% vs. 41.8%, $P = 0.993$) were similar between the bridging therapy and direct EVT groups. The risk of symptomatic ICH in the bridging therapy group was lower than in the direct EVT group (9.8% vs. 14.4%, $P = 0.198$), but didn't reach statistically significant.

After adjusting for covariates, no significant differences were found in the risks of any ICH, symptomatic ICH, or 90-day mortality between the bridging therapy and direct EVT groups, the 'drip-and-ship' and direct EVT groups, the 'mothership' and direct EVT groups, and the 'drip-and-ship' and 'mothership' groups (Fig. 2).

Compared with direct EVT, bridging therapy was linked to a lower risk of any ICH in patients with admission NIHSS scores of 20 or higher [IPW-adjusted OR = 0.791 (95% CI, 0.657–0.952)] and in those with pre-treatment ASPECTS of 0 to 2 [IPW-adjusted OR = 0.808 (95% CI, 0.669–0.976)]. The admission NIHSS score significantly influenced the relationship between IVT and the occurrence of any ICH (IPW-adjusted P value for interaction = 0.003), as detailed in Supplementary Table 5, Supplemental Digital Content 2, http://links.lww.com/JS9/D333. Further investigation into the NIHSS score threshold revealed that at an admission NIHSS of 22 or higher, the entire 95% CIs for the impact of IVT on the risk of any ICH remained below 1.0. This observation suggested that IVT may be associated with a reduced risk of ICH in patients with admission NIHSS scores of 22 or higher (Fig. 3).

Additionally, the bridging therapy was associated with the decreased risks of symptomatic ICH in various patient subgroups, including the very elderly [IPW-adjusted OR = 0.913 (95% CI, 0.847–0.984)], male (IPW-adjusted OR = 0.935 (95% CI, 0.878 - 0.997)], those with very low ASPECTS [IPW-adjusted OR = 0.873 (95% CI, 0.790 - 0.966)], current smokers [IPW-adjusted OR = 0.901 (95% CI, 0.853–0.952)], individuals with

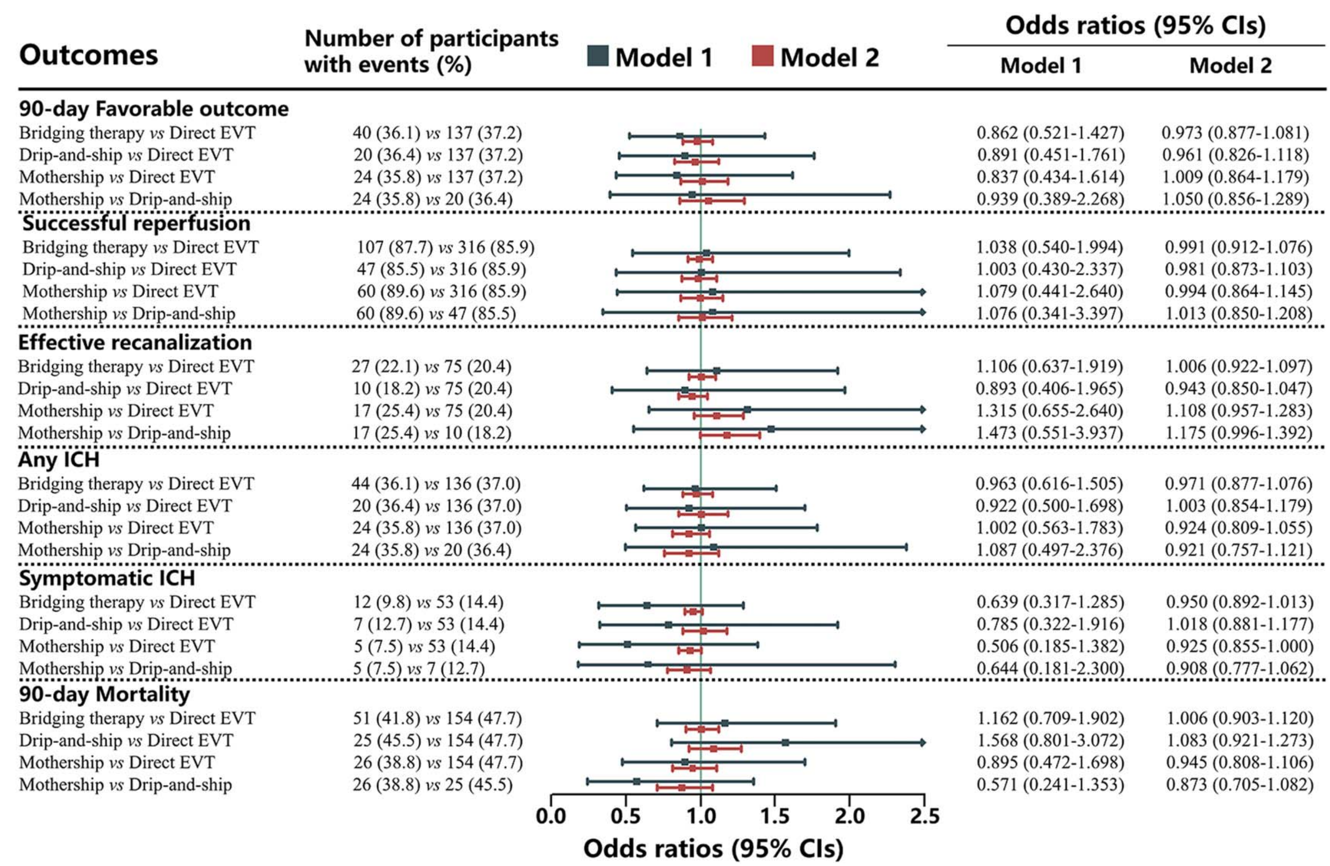

Figure 2. Forest plot showing the comparison of clinical outcomes between bridging therapy and direct endovascular thrombectomy groups. The odds ratios and 95% CIs depicted reflect the comparison of clinical outcomes for large core infarction patients who received bridging therapy versus those who received direct endovascular thrombectomy (EVT). Model 1 was unweighted multivariable-adjusted logistic regression and Model 2 was inverse probability weighting (IPW) adjusted logistic regression. ICH, intracranial hemorrhage.

hypertension [IPW-adjusted OR = 0.898 (95% CI, 0.847–0.951)], left hemisphere infarction [IPW-adjusted OR = 0.899 (95% CI, 0.829–0.976)], without atrial fibrillation [IPW-adjusted OR = 0.919 (95% CI, 0.855–0.987)], and without hyperlipidemia [IPW-adjusted OR = 0.929 (95% CI, 0.866–0.997)] (Supplementary Table 6, Supplemental Digital Content 2, http://links.lww.com/JS9/D333). However, the effect modification of age, sex, ASPECTS, hypertension, infarcted hemisphere, atrial fibrillation, and hyperlipidemia on the relationship between IVT and symptomatic ICH did not reach statistical significance (Supplementary Table 6, Supplemental Digital Content 2, http://links.lww.com/JS9/D333). Furthermore, IVT wasn't associated with the 90-day mortality in any of the subgroups, and no covariate influenced the association between IVT and 90-day mortality (Supplementary Table 7, Supplemental Digital Content 2, http://links.lww.com/JS9/D333).

Sensitivity analysis

To assess the stability of the results and to aid in determining whether patients should initially receive bridging therapy or proceed directly to EVT within the first 4.5 h of symptom onset, we conducted a sensitivity analysis. This analysis included all patients in the bridging therapy group ($n = 122$) and those in the direct EVT group ($n = 109$) who had a puncture time within 4.5 h after the last known well. The adjusted odds of 90-day favorable outcomes, successful reperfusion, effective recanalization, any ICH, symptomatic ICH, and 90-day mortality were similar across the bridging therapy and direct EVT groups, the 'drip-and-ship' and direct EVT groups, as well as the 'mothership' and direct EVT groups, and between the 'drip-and-ship' and 'mothership' groups (Supplementary Table 8, Supplemental Digital Content 2, http://links.lww.com/JS9/D333 and Supplementary Fig. 2, Supplemental Digital Content 2, http://links.lww.com/JS9/D333). Moreover, in line with the analysis of subgroups in the main study population, bridging therapy was associated with a reduced risk of any ICH in patients with admission NIHSS scores of 20 or higher [IPW-adjusted OR = 0.757 (95% CI, 0.602–0.953)], and the admission NIHSS continued to significantly modify the relationship between IVT and any ICH in the sensitivity analysis sample (IPW-adjusted *P* value for interaction = 0.007) (Supplementary Table 9 -14, Supplemental Digital Content 2, http://links.lww.com/JS9/D333). Additionally, bridging therapy was associated with a decreased risk of symptomatic ICH in very elderly patients [IPW-adjusted OR = 0.866 (95% CI, 0.753–0.995)], reaffirming the results observed in the subgroup analysis of the main study population (Supplementary Table 13, Supplemental Digital Content 2, http://links.lww.com/JS9/D333).

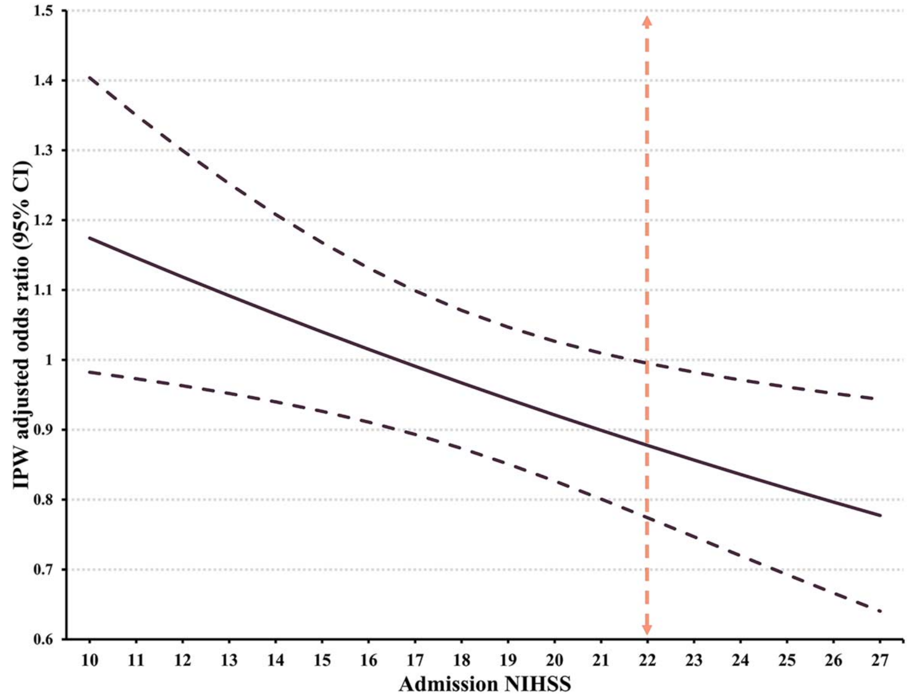

Figure 3. The odds ratio for the favorable outcomes at 3 months in bridging therapy versus direct endovascular thrombectomy groups by admission stroke severity. The odds ratios and 95% CIs were obtained from inverse probability weighting (IPW) adjusted logistic regression of any intracranial hemorrhage on admission National Institutes of Health Stroke Scale (NIHSS) as a continuous variable. The propensity score was estimated using a non-parsimonious multivariable logistic regression model with the treatment group as the dependent variable and including all selected covariates. When the admission NIHSS score is 22, the upper bound of the confidence interval begins to fall below 1.0.

In contrast, the risk of symptomatic ICH between bridging therapy and direct EVT within 4.5 h showed no significant difference for several subgroups: male patients, those with pretreatment ASPECTS scores between 0 and 2, current smokers, patients with hypertension, patients with left hemisphere infarction, those without atrial fibrillation, and those without hyperlipidemia (Supplementary Table 13, Supplemental Digital Content 2, http://links.lww.com/JS9/D333). The likelihood of achieving effective recanalization between bridging therapy and direct EVT also showed no significant difference for very elderly patients or those with good collaterals (Supplementary Table 11, Supplemental Digital Content 2, http://links.lww.com/JS9/D333). Notably, the sensitivity analysis revealed a lower 90-day mortality in the bridging therapy group compared to the direct EVT group treated within 4.5 h [IPW-adjusted OR = 0.755 (95% CI, 0.578–0.985)], a finding that was not statistically significant in the main study population (Supplementary Table 14, Supplemental Digital Content 2, http://links.lww.com/JS9/D333).

Discussion

In this multicenter cohort study, we explored the association between prior IVT use and the outcomes of large core infarctions with EVT treatment. In line with the subgroup analyses from recently published RCTs for patients with LVO[9–11], our research findings suggested that prior IVT use overall did not significantly impact the odds of favorable 90-day outcomes, successful reperfusion, effective recanalization, or the risk of any ICH, symptomatic ICH, and 90-day mortality in patients with large core infarctions treated with EVT.

Results from meta-analyses of RCTs suggest that among patients with AIS due to LVO who qualify for IVT and are directly admitted to a facility equipped for EVT, the likelihood of achieving favorable functional outcomes and the incidence of adverse safety events are similar for those receiving bridging therapy compared to direct EVT alone[21–26]. However, the bridging therapy group demonstrated higher rates of successful reperfusion[35].

In this multicenter study, we observed that sICH occurred in 13.7% of patients, which is significantly higher than the 3.2% reported in RCTs[36]. Previous RCT studies on large core infarcts mostly included patients with ASPECTS of 3–5. In contrast, our study included patients with ASPECTS of 0–5, with 27.6% having scores of 0–2. Due to rapid arterial occlusion, cardioembolic stroke usually results in a smaller penumbra and a larger core infarct[37], which may increase the risk of ICH[38]. These factors may explain why the proportion of sICH in our study is higher than in prior RCTs.

Currently, evidence from RCTs specifically addressing the relative efficacy and safety of bridging therapy versus direct EVT in the early management of large core infarctions is absent, with the available results from observational studies being both sparse and inconclusive. A retrospective analysis from two high-volume tertiary stroke centers has shown that the prior application of IVT in thrombectomy patients with low ASPECTS might have a detrimental effect on functional outcomes[39]. Broocks and colleagues suggest that bridging IVT in patients with low ASPECTS was associated with very poor functional outcomes[40]. Additionally, a significant safety consideration for the combined use of IVT is the risk of ICH since both EVT and IVT carry a risk independently. The multicenter cohort study BEYOND-SWIFT (Bernese-European Registry for Ischemic Stroke Patients Treated Outside Current Guidelines With Neurothrombectomy Devices Using the SOLITAIRE FR With the Intention for Thrombectomy) indicated that, across different patient groups with varying ASPECTS, the risk of symptomatic ICH differs between patients treated with combined IVT plus EVT and those receiving direct EVT[41]. Subanalysis results from the RESCUE-Japan LIMIT study suggest that for patients with large core infarcts, the likelihood of favorable outcomes of bridging therapy is similar to that of direct EVT, but bridging therapy significantly increases the risk of symptomatic ICH[42]. However, this study did not include patients with very low ASPECTS (0–2). Recently, a retrospective analysis of data from the ETIS (Endovascular Treatment in Ischemic Stroke) Registry has presented a different conclusion: treatment with IVT before EVT appeared to provide a clinical benefit, in terms of being associated with greater odds of good procedural and functional outcomes, with no increased risks of either ICH or death, compared with treatment with direct EVT[43].

In many subgroups of our study, prior use of IVT was linked with lower risks of symptomatic ICH. It is noteworthy that the prior use of IVT reduced the risk of any ICH and symptomatic ICH in patients with very large core infarctions undergoing thrombectomy (ASPECTS 0 to 2, $n = 135$), a subgroup that has not been sufficiently studied. However, compared to patients undergoing direct thrombectomy within 4.5 h, bridging therapy did not demonstrate an advantage in reducing ICH in this specific subgroup. This may also be due to the smaller sample size of the sensitivity analysis, which resulted in insufficient statistical power. Therefore, further research is needed to verify whether bridging therapy can reduce the risk of hemorrhage in patients with very large core infarctions. Moreover, irrespective of whether patients received direct EVT within 4.5 h, bridging IVT was significantly associated with a lower risk of symptomatic ICH in patients aged 80 and older. Nevertheless, considering the potential bias due to the low incidence rate of symptomatic ICH, these results necessitate further validation through additional studies.

Additionally, although any ICH after EVT may not lead to a rapid worsening of symptoms as symptomatic ICH does, it nonetheless postpones the opportunity to initiate antiplatelet therapy post-procedure. Our analysis suggests that regardless of whether the puncture time of direct EVT is within 4.5 h, bridging therapy was significantly associated with a lower risk of any ICH in patients with severe stroke (admission NIHSS $\geq$ 20), early stroke severity may alter the odds of any ICH in patients with bridging therapy versus direct EVT. Specifically, among patients with admission NIHSS score of 22 or higher, prior IVT use is associated with a reduced risk of any ICH. This could be because IVT can increase early reperfusion, enhance perfusion to the brain's remote territories, reduce the number of required EVT passes, and decrease the occurrence of impaired microvascular reperfusion. These results suggest that administering IVT before EVT in patients with ASPECTS 0–2 or an NIHSS greater than 20 may reduce the risk of post-thrombectomy hemorrhage. This provides potential support for individualized reperfusion therapy, but this conclusion still needs to be validated by future RCT studies.

Limitation

Firstly, this research is an observational study and lacks a randomization process; therefore, some biases are inevitable. However, the study, through its large sample size, multicenter approach, and prospective design, also reflects real-world treatment conditions. Secondly, some patients initially considered for EVT may have been excluded due to post-thrombolysis hemorrhage or symptom improvement. Therefore, it may be inaccurate to estimate the effectiveness and safety of selecting IVT as the initial therapy. Further specialized RCT studies are needed for validation in the future. Thirdly, some subgroups had small sample sizes, which may have limited the statistical power of the study, but we mitigated this limitation to some extent through inverse probability weighting.

Conclusion

Overall, we did not observe any benefit of bridging therapy over direct thrombectomy in patients with large core infarctions, nor did we find that bridging therapy increased the risk of safety events in these patients. Interestingly, in certain subgroups, bridging therapy was associated with a reduced risk of both any ICH and symptomatic ICH. Administering IVT before EVT in individuals with an ASPECTS score of 0–2 or an NIHSS score exceeding 20 may lower the risk of hemorrhage following thrombectomy. This provides potential insights into reperfusion strategies for large core infarctions. However, this finding still requires confirmation through future RCTs.

Ethical approval

The study was approved by the ethics committees of the Second Affiliated Hospital of the Army Medical University and participating hospitals (ChiCTR2100051664).

Consent

All enrolled patients or their legally authorized representatives provided written informed consent before enrollment.

Source of funding

This work was supported by the Youth Doctoral Talent Incubation Program of Second Affiliated Hospital of the Army Medical University (2023YQB065), and Chongqing Science and Health Joint Project (2024MSXM006).

Author contribution

J.H.: had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; W.S., J.M., M.Z., and J.H.: concept and design; W.S., X.X., and Y.Z.: acquisition, analysis, or interpretation of data; W.S., J.M., X.X., and Y.Z.: draughting of the manuscript; L.Z., N.Y., and C.Y.: critical revision of the manuscript for important intellectual content; W.S., J.C., and C.G.: statistical analysis; W.Z.: obtained funding; M.Z., and Z.H.: supervision.

Conflicts of interest disclosure

All authors declare no conflict of interest.

Research registration unique identifying number (UIN)

The data of this study was obtained from a prospective, multicenter cohort study of early treatment in acute stroke. URL: http://www.chictr.org.cn. Unique identifier: ChiCTR2100051664.

Guarantor

The guarantors are Jinzhao He and Minzhen Zhu.

Data availability statement

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Berkhemer OA, Fransen PS, Beumer D, *et al*. A randomized trial of intraarterial treatment for acute ischemic stroke. N Eng J Med 2015;372: 11–20.
[2] Saver JL, Goyal M, Bonafe A, *et al*. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Eng J Med 2015;372: 2285–95.
[3] Jovin TG, Chamorro A, Cobo E, *et al*. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Eng J Med 2015;372: 2296–306.
[4] Goyal M, Demchuk AM, Menon BK, *et al*. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Eng J Med 2015;372: 1019–30.
[5] Campbell BC, Mitchell PJ, Kleinig TJ, *et al*. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Eng J Med 2015;372: 1009–18.
[6] Nogueira RG, Jadhav AP, Haussen DC, *et al*. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Eng J Med 2018;378:11–21.
[7] Albers GW, Marks MP, Kemp S, *et al*. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Eng J Med 2018;378: 708–18.
[8] Powers WJ, Rabinstein AA, Ackerson T, *et al*. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2019;50:e344–418.
[9] Sarraj A, Hassan AE, Abraham MG, *et al*. Trial of endovascular thrombectomy for large ischemic strokes. N Eng J Med 2023;388: 1259–71.
[10] Huo X, Ma G, Tong X, *et al*. Trial of endovascular therapy for acute ischemic stroke with large infarct. N Eng J Med 2023;388:1272–83.
[11] Yoshimura S, Sakai N, Yamagami H, *et al*. Endovascular therapy for acute stroke with a large ischemic region. N Eng J Med 2022;386: 1303–13.
[12] Bendszus M, Fiehler J, Subtil F, *et al*. Endovascular thrombectomy for acute ischaemic stroke with established large infarct: multicentre, open-label, randomised trial. Lancet (London, England) 2023;402:1753–63.
[13] Goyal M, Menon BK, van Zwam WH, *et al*. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet (London, England) 2016;387: 1723–31.
[14] Behme D, Kabbasch C, Kowoll A, *et al*. Intravenous thrombolysis facilitates successful recanalization with stent-retriever mechanical thrombectomy in middle cerebral artery occlusions. J Stroke Cerebrovasc Dis 2016;25:954–9.
[15] Desilles JP, Loyau S, Syvannarath V, *et al*. Alteplase reduces downstream microvascular thrombosis and improves the benefit of large artery recanalization in stroke. Stroke 2015;46:3241–8.
[16] Seners P, Turc G, Naggara O, *et al*. Post-thrombolysis recanalization in stroke referrals for thrombectomy: incidence, predictors, and prediction scores. Stroke 2018;49:2975–82.
[17] Goyal N, Tsivgoulis G, Pandhi A, *et al*. Impact of pretreatment with intravenous thrombolysis on reperfusion status in acute strokes treated with mechanical thrombectomy. J Neurointervent Surg 2019;11:1073–9.
[18] Derraz I. The end of tissue-type plasminogen activator's reign? Stroke 2022;53:2683–94.
[19] Ren Y, Churilov L, Mitchell P, *et al*. Clot migration is associated with intravenous thrombolysis in the setting of acute ischemic stroke. Stroke 2018;49:3060–2.
[20] Yaghi S, Eisenberger A, Willey JZ. Symptomatic intracerebral hemorrhage in acute ischemic stroke after thrombolysis with intravenous recombinant tissue plasminogen activator: a review of natural history and treatment. JAMA Neurol 2014;71:1181–5.
[21] LeCouffe NE, Kappelhof M, Treurniet KM, *et al*. A randomized trial of intravenous alteplase before endovascular treatment for stroke. N Eng J Med 2021;385:1833–44.
[22] Fischer U, Kaesmacher J, Strbian D, *et al*. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. Lancet (London, England) 2022;400:104–15.
[23] Mitchell PJ, Yan B, Churilov L, *et al*. Endovascular thrombectomy versus standard bridging thrombolytic with endovascular thrombectomy within 4·5 h of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. Lancet (London, England) 2022;400: 116–25.
[24] Zi W, Qiu Z, Li F, *et al*. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: The DEVT Randomized Clinical Trial. JAMA 2021;325:234–43.
[25] Yang P, Zhang Y, Zhang L, *et al*. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. N Eng J Med 2020;382: 1981–93.
[26] Suzuki K, Matsumaru Y, Takeuchi M, *et al*. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: The SKIP Randomized Clinical Trial. JAMA 2021;325:244–53.
[27] Jones TH, Morawetz RB, Crowell RM, *et al*. Thresholds of focal cerebral ischemia in awake monkeys. J Neurosurg 1981;54:773–82.
[28] Mathew G, Agha R. ftSG. STROCSS 2021: Strengthening the Reporting of cohort, cross-sectional and case-control studies in Surgery. Int J Surg 2021;96:106165.
[29] Guo C, Li L, Huang J, *et al*. Endovascular treatment versus standard medical treatment in patients with established large infarct: a cohort study. Int J Surg 2024;110:4775–84.
[30] Regenhardt RW, Rosenthal JA, Awad A, *et al*. Drip-and-ship' intravenous thrombolysis and outcomes for large vessel occlusion thrombectomy candidates in a hub-and-spoke telestroke model. J Neurointervent Surg 2022;14:650–3.
[31] Meyer L, Bechstein M, Bester M, *et al*. Thrombectomy in extensive stroke may not be beneficial and is associated with increased risk for hemorrhage. Stroke 2021;52:3109–17.
[32] Winkelmeier L, Broocks G, Kniep H, *et al*. Venous outflow profiles are linked to clinical outcomes in ischemic stroke patients with extensive baseline infarct. J Stroke 2022;24:372–82.
[33] Broocks G, Kniep H, Schramm P, *et al*. Patients with low Alberta Stroke Program Early CT Score (ASPECTS) but good collaterals benefit from endovascular recanalization. J Neurointervent Surg 2020;12:747–52.
[34] von Kummer R, Broderick JP, Campbell BC, *et al*. The Heidelberg Bleeding Classification: classification of bleeding events after ischemic stroke and reperfusion therapy. Stroke 2015;46:2981–6.
[35] Trifan G, Biller J, Testai FD. Mechanical thrombectomy vs bridging therapy for anterior circulation large vessel occlusion stroke: systematic review and meta-analysis. Neurology 2022;98:e1361–73.

[36] Kobeissi H, Adusumilli G, Ghozy S, *et al*. Endovascular thrombectomy for ischemic stroke with large core volume: an updated, post-TESLA systematic review and meta-analysis of the randomized trials. Interv Neuroradiol 2023. doi:10.1177/15910199231185738.
[37] Kim SJ, Seok JM, Bang OY, *et al*. MR mismatch profiles in patients with intracranial atherosclerotic stroke: a comprehensive approach comparing stroke subtypes. J Cereb Blood Flow Metab 2009;29:1138–45.
[38] Albers GW, Thijs VN, Wechsler L, *et al*. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. Ann Neurol 2006;60:508–17.
[39] Broocks G, Heit JJ, Kuraitis GM, *et al*. Benefit of intravenous alteplase before thrombectomy depends on ASPECTS. Ann Neurol 2022;92: 588–95.
[40] Broocks G, McDonough R, Bechstein M, *et al*. Benefit and risk of intravenous alteplase in patients with acute large vessel occlusion stroke and low ASPECTS. J Neurointervent Surg 2023;15:8–13.
[41] Kaesmacher J, Meinel TR, Nannoni S, *et al*. Bridging may increase the risk of symptomatic intracranial hemorrhage in thrombectomy patients with low alberta stroke program early computed tomography score. Stroke 2021;52:1098–104.
[42] Shindo S, Uchida K, Yoshimura S, *et al*. Intravenous alteplase before endovascular therapy for acute large vessel occlusion with large ischemic core: subanalysis of a randomized clinical trial. J Neurointervent Surg 2023. doi:10.1136/jnis-2023-020846.
[43] Derraz I, Moulin S, Gory B, *et al*. Endovascular thrombectomy outcomes with and without intravenous thrombolysis for large ischemic cores identified with CT or MRI. Radiology 2023;309:e230440.