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Effect of bleeding risk prediction on decision making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

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ABSTRACT

Background The major concern for bridging intravenous thrombolysis (IVT) before endovascular thrombectomy (EVT) is the potentially increased risk of symptomatic intracerebral hemorrhage (sICH). Thus we conducted this study to clarify whether evaluation of individual bleeding risk could assist in the decision to perform IVT before EVT.

Methods The study was a subgroup analysis of a randomized trial evaluating the safety and efficacy of IVT before EVT. The SEDAN (blood Sugar, Early infarct signs and (hyper) Dense cerebral artery sign, Age, and National Institutes of Health Stroke Score) score, GRASPS (Glucose, Race, Age, Sex, systolic blood Pressure, and Severity of stroke) score, and SITS-SICH (Safe Implementation of Thrombolysis in Stroke-Symptomatic Intracerebral Hemorrhage) score were used to evaluate individual bleeding risk. The primary outcome was functional independence, defined as a modified Rankin Scale (mRS) score of 0–2 at 90 days. Binary logistic regression with an interaction term was used to estimate treatment effect modification to clarify whether direct EVT was more beneficial in patients with a higher sICH risk, while adjunctive IVT before EVT was more beneficial in patients with a lower sICH risk.

Results Among 658 randomized patients, 639 (361 men, 56.5%; median age 69 (IQR 61–76) years) were included in the study. With the SITS-SICH score as an example, adjusted OR for functional independence with EVT alone was 1.12 (95% CI 0.68 to 1.82) in patients with a lower sICH risk (SITS-SICH score 0–4) and 0.92 (0.53 to 1.60) in those with a higher sICH risk (SITS-SICH score 5–15). There were no treatment-by-bleeding-risk interactions for all dichotomized mRS outcomes based on the three scores (all $p > 0.05$).

Conclusions We found no evidence that clinicians can decide whether to omit IVT before EVT based on an individualized assessment of bleeding risk.

INTRODUCTION

Endovascular thrombectomy (EVT) has become the standard of care for patients with acute ischemic stroke due to large vessel occlusion in the anterior circulation.¹ Current guidelines also recommend intravenous thrombolysis (IVT) before EVT in eligible patients.^{2,3} The potential advantage of IVT

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several randomized trials have recently investigated the adjunctive benefit of intravenous thrombolysis (IVT) before endovascular thrombectomy (EVT) by using non-inferiority designs, with mixed results in supporting or refuting the benefits.

WHAT THIS STUDY ADDS

⇒ Patients with a higher bleeding risk did not benefit more from EVT alone than bridging therapy, while those with a lower bleeding risk did not benefit more from bridging therapy than EVT alone.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ We found no evidence that clinicians can decide whether to omit IVT before EVT based on an individualized assessment of bleeding risk.

prior to EVT is that alteplase can partially dissolve the thrombi, achieving earlier and more complete recanalization, especially in cases of delay in EVT.^{4,5} In contrast, administration of alteplase might delay initiation of the EVT procedure, and increase the risk of intracranial hemorrhage (ICH) and medical expenses.⁶

Several randomized trials,^{7–12} including DIRECT-MT (Direct Intra-arterial Thrombectomy in Order to Revascularize AIS Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals),⁷ have recently investigated the adjunctive benefit of IVT before EVT by using non-inferiority designs, with mixed results in supporting or refuting the benefits. Since outcomes were similar for both treatment arms across the published trials,¹³ the heterogeneity of the treatment effect of IVT on subgroups based on patient characteristics is worth exploring further. The major concern for bridging IVT is the increased risk in symptomatic intracerebral hemorrhage (sICH). Hence we hypothesized that evaluation of individual bleeding risk could assist in the decision to perform IVT before EVT.

Because both treatment arms received EVT, we used a prediction scale of bleeding risk for IVT

alone, to separately evaluate the bleeding risk from IVT. There are several scoring systems available to predict the risk of sICH after IVT.^{14–19} Three scores have better reliability and validity due to the large sample size of both the derivation and validation cohorts.^{16–18} Based on these scores, we aimed to investigate whether direct EVT was more beneficial in patients with a higher risk of sICH, and whether adjunctive IVT before EVT was more beneficial in patients with a lower risk of sICH, in this subgroup analysis of DIRECT-MT.

METHODS

Study design and patients

DIRECT-MT was a randomized, controlled, open label trial, assessing the non-inferiority of EVT alone versus bridging therapy (IVT before EVT) in patients from 41 centers in China. Patients were aged ≥ 18 years with a proximal arterial occlusion in the anterior circulation, and treated within 4.5 hours of symptom onset. Detailed study methods and patient eligibility criteria have been reported previously.^{7 20} In this subgroup analysis, those who did not undergo catheter angiography were excluded. Written informed consent was obtained from all patients or their legal representatives before randomization. The study protocol was approved by a central medical ethics committee and the research board of each participating center.

Procedure

Demographic, laboratory, radiological, and clinical characteristics were recorded at the time of enrollment. Imaging was evaluated by an independent imaging core laboratory that was blinded to the treatment assignments, with a consensus reached in the event of discrepancies. Collateral flow was graded with baseline CT angiography, using a 4 point scale, with 0 representing absent collateral flow (absent filling of the occluded territory), 1 representing poor collateral flow ($<50\%$ filling of the occluded territory), 2 representing intermediate collateral flow (between 50% and 100% filling of the occluded territory), and 3 representing excellent collateral flow (100% filling of the occluded territory). Outcome data at 3 months were obtained from structured interviews using standardized forms, and were then verified with the score on the modified Rankin Scale (mRS) by an outcome committee.

Three scores were used to evaluate individual bleeding risk. The SEDAN (blood Sugar, Early infarct signs and (hyper)Dense cerebral artery sign, Age, and National Institutes of Health Stroke Score (NIHSS)) score (range 0–6) included baseline glucose (1 point for 145–216 mg/dL and 2 points for >216 mg/dL), early infarct signs (1 point), hyperdense cerebral artery sign (1 point), age (1 point for >75 years), and baseline NIHSS score (1 point for ≥ 10).¹⁶ The GRASPS (Glucose, Race, Age, Sex, systolic blood Pressure, and Severity of stroke) score (range 45–105) included baseline glucose (2 points for <100 mg/dL, 6 points for 100–149 mg/dL, and 8 points for ≥ 150 mg/dL), ethnicity (9 points for Asian), age (8 points for ≤ 60 years, 11 points for 61–70 years, 15 points for 71–80 years, and 17 points for >80 years), gender (4 points for men), baseline systolic blood pressure (10 points for <120 mm Hg, 14 points for 120–149 mm Hg, 18 points for 150–179 mm Hg, and 21 points for ≥ 180 mmHg), and baseline NIHSS score (25 points for 0–5, 27 points for 6–10, 34 points for 11–15, 40 points for 16–20, and 42 points for >20).¹⁷ The SITS-SICH (Safe Implementation of Thrombolysis in Stroke-Symptomatic Intracerebral Hemorrhage) score (range 0–15) included baseline NIHSS score (1 point for 7–12 and 2 points for >12), baseline glucose (2 points for >180 mg/dL),

baseline systolic blood pressure (1 point for ≥ 146 mm Hg), age (1 point for 72 years), body weight (1 point for ≥ 95 kg), onset to treatment time (1 point for ≥ 180 min), prior antiplatelet therapy (2 points for aspirin monotherapy and 3 points for combined aspirin and clopidogrel), and history of hypertension (1 point).¹⁸ The cut-off value for each score was determined by the relatively balanced sample size in both groups, while considering approximately 10% of predicted sICH (European Cooperative Acute Stroke Study (ECASS II) criteria) risk in the high bleeding risk group based on data from previous studies.^{16–18 21}

Outcome assessment

The primary outcome of this subgroup analysis was functional independence defined as an mRS score of 0–2 at 90 days (within a window of ± 14 days) after randomization. Secondary outcomes were the following: favorable functional outcome (defined as an mRS score of 0–1 at 90 days after randomization), successful reperfusion (defined as an extended Thrombolysis in Cerebral Infarction score of $\geq 2b$) before thrombectomy (assessed on initial DSA),²² and successful reperfusion on final DSA. Safety outcomes were sICH and asymptomatic ICH according to the Heidelberg criteria,²³ assessed on follow-up non-contrast CT at 24–72 hours, and mortality within 90 days.

Statistical analysis

The analyses were primarily based on the as-treated population. Study participants were dichotomized according to the prediction scores of sICH risk. Data are presented as mean (SD), median (IQR), or number (%). The χ^2 test or Fisher's exact test was used to compare the dichotomous variables between groups, while the independent sample t test or Mann–Whitney U test was used for continuous variables, as appropriate. We analyzed binary outcomes with logistic regression and reported them as both unadjusted and adjusted ORs with 95% CIs, for age, baseline NIHSS score, baseline mRS score, time from stroke onset to randomization, and cerebral collateral status per the DIRECT-MT statistical analysis plan. Statistical significance was set at a p value of <0.05 . All statistical analyses were performed with SAS software, version 9.2 (SAS Institute).

RESULTS

The trial profile of the subgroup analyses is shown in [figure 1](#). A total of 656 patients were randomized in the DIRECT-MT trial between February 23, 2018 and July 2, 2019. Seventeen patients did not undergo catheter angiography and thus were excluded from the subgroup analyses. Finally, 639 patients (361 men (56.5%); median age 69 (IQR 61–76) years), 316 (49.5%) in the EVT alone group and 323 (50.5%) in the bridging therapy group, were included. Median baseline NIHSS score was 17 (IQR 13–22) and mean time interval from stroke onset to puncture was 204.9 ± 58.8 min.

Comparison of actual sICH rate and predicted sICH risk

[Table 1](#) shows the comparison of sICH rate in patients with a high or low predicted sICH risk (for IVT) based on the SEDAN, GRASPS, and SITS-SICH scores. In the whole cohort, more sICH occurred in patients who had a higher score, with significant or marginally significant difference. Regardless of treatment approach and rating scale, the sICH rate was numerically higher in patients who had a higher score, although this was not statistically significant.

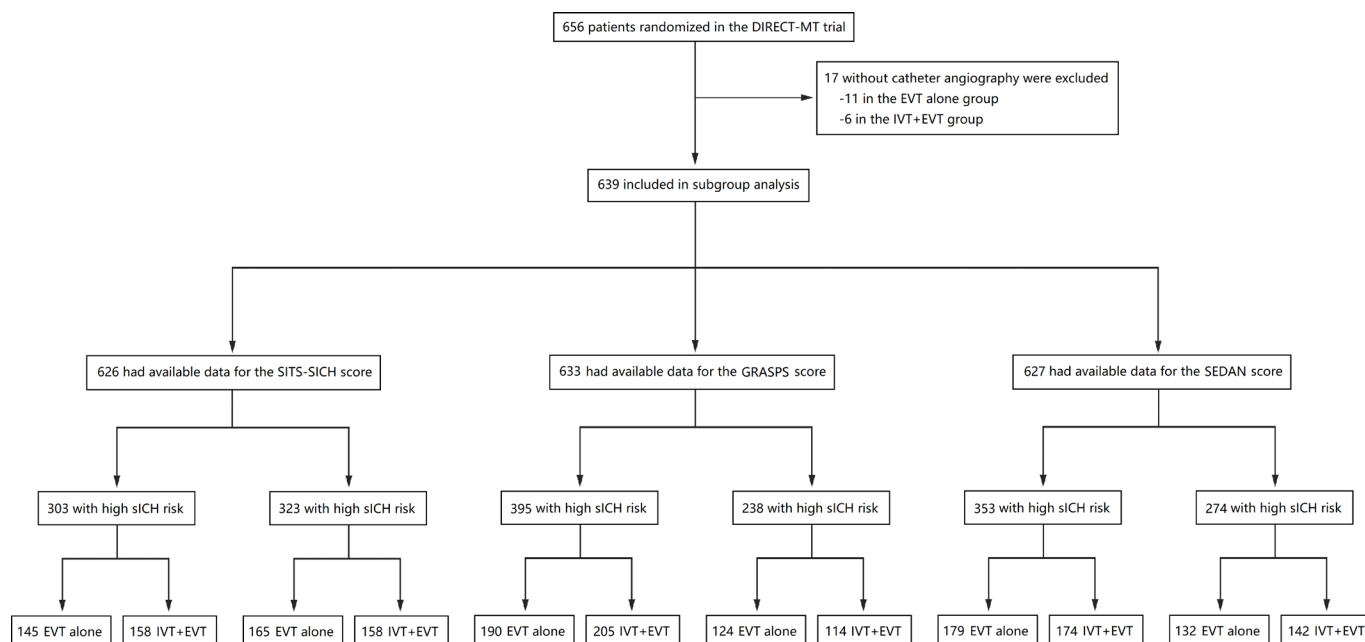


Figure 1 Trial profile of the subgroup analyses. Patients with a higher bleeding risk were defined as a SEDAN (blood Sugar, Early infarct signs and (hyper)Dense cerebral artery sign, Age, and National Institutes of Health Stroke Score) score of ≥ 3 , GRASPS (Glucose, Race, Age, Sex, systolic blood Pressure, and Severity of stroke) score of >80 , or SITS-SICH (Safe Implementation of Thrombolysis in Stroke-Symptomatic Intracerebral Hemorrhage) score of ≥ 5 . EVT, endovascular treatment; IVT, intravenous thrombolysis; sICH symptomatic intracranial hemorrhage.

Comparison of characteristics stratified by sICH risk prediction score

Baseline characteristics of the enrolled cohort, stratified by SITS-SICH score, are shown in [table 2](#). A total of 626 patients had available data for the SITS-SICH score, among whom 323 (51.6%) were rated as having a SITS-SICH score of 0–4 (165 (51.1%) received EVT alone; 158 (48.9%) received bridging therapy) and 303 (48.4%) a score of 5–15 (145 (47.9%) received EVT alone; 158 (52.1%) received bridging therapy). Baseline characteristics were similar in the treatment groups stratified by SITS-SICH risk score, except that the time interval from onset to puncture was shorter and the presence of early infarct sign was more often in patients who received EVT alone and had a higher SITS-SICH score, with marginally significant differences ([table 2](#)). Similar findings for SEDAN and GRASPS scores are shown in online supplemental tables 1 and 2.

Primary outcome

The mRS score at 90 days was missing for two patients (one received EVT alone and one received bridging therapy), and data were not imputed. Patients who were rated as having an SITS-SICH score of 5–15 achieved a lower rate of functional independence than those rated as having a score of 0–4 (80 (26.5%) vs 151 (46.7%), $p < 0.001$). The adjusted OR for functional independence with EVT alone was 1.12 (95% CI 0.68 to 1.82) in patients with a lower SITS-SICH score (0–4), and 0.92 (95% CI 0.53 to 1.60) in those with a higher SITS-SICH score (5–15) ([table 3](#)). The adjusted OR for functional independence with EVT alone was 1.00 (95% CI 0.58 to 1.71) in patients with a lower SEDAN score (0–2), and 1.14 (95% CI 0.69 to 1.88) in those with a higher SEDAN score (3–6) (online supplemental table 3). The adjusted OR for functional independence with EVT alone was 1.20 (95% CI 0.69 to 2.06) in patients with a lower GRASPS score (45–80), and 0.88 (95% CI 0.54 to 1.43) in those with a higher GRASPS score (81–105) (online supplemental table 4). There were no treatment-by-bleeding-risk interactions

for all dichotomized mRS outcomes based on the three scores, in both adjusted and unadjusted analysis ([table 4](#)).

Secondary and safety outcomes

The adjusted ORs and 95% CIs for the secondary and safety outcomes stratified by SITS-SICH score are shown in [table 3](#). For the majority of secondary and safety outcomes, such as favorable functional outcome, successful reperfusion after EVT, death, and sICH, no significant differences were found between the EVT alone group and the bridging therapy group, stratified by SITS-SICH risk score. Successful reperfusion before EVT (3 (2.1%) vs 13 (8.3%); OR 0.27, 95% CI 0.07 to 0.99) and asymptomatic ICH (44 (30.3%) vs 73 (46.2%); OR 0.53, 95% CI 0.33 to 0.87) occurred less frequently in patients who received EVT alone and had a higher SITS-SICH score ([table 3](#)). The adjusted ORs and 95% CIs for the secondary and safety outcomes stratified by SEDAN and GRASPS scores are shown in online supplemental tables 3 and 4.

DISCUSSION

In this subgroup analysis, we found no evidence of treatment effect modification by predicted sICH risk for functional outcome, based on the SEDAN, GRASPS, and SITS-SICH scores. Specifically, patients with a higher bleeding risk did not benefit more from EVT alone than bridging therapy, while those with a lower bleeding risk did not benefit more from bridging therapy than EVT alone.

The results of six recent randomized trials that compared the effect of EVT alone versus bridging therapy were inconsistent.^{7–12} The DIRECT-MT and DEVT (Direct Endovascular Treatment vs Standard Bridging Therapy for Patients With Acute Stroke With Large Vessel Occlusion in the Anterior Circulation) trials,^{7,8} both from China, showed that EVT alone was non-inferior to alteplase followed by EVT, with liberal non-inferiority margins. The SKIP (Direct Mechanical Thrombectomy in Acute LVO Stroke) trial,⁹ conducted in Japan, was underpowered and did not show the

Table 1 Comparison of symptomatic intracerebral hemorrhage rate in patients with a high or low predicted risk of symptomatic intracerebral hemorrhage after intravenous thrombolysis, based on the three scores

		sICH (n (%))	No sICH (n (%))	P value
Entire cohort				
SEDAN score	0–2 (n=274)	10 (3.6)	264 (96.4)	0.084
	3–6 (n=353)	24 (6.8)	329 (93.2)	
GRASPS score	45–80 (n=238)	7 (2.9)	231 (97.1)	0.035
	81–105 (n=395)	27 (6.8)	368 (93.2)	
SITS-SICH score	0–4 (n=323)	12 (3.7)	311 (96.3)	0.072
	5–15 (n=303)	21 (6.9)	282 (93.1)	
Patients with EVT alone				
SEDAN score	0–2 (n=132)	3 (2.3)	129 (97.7)	0.104
	3–6 (n=179)	11 (6.1)	168 (93.9)	
GRASPS score	45–80 (n=124)	2 (1.6)	122 (98.4)	0.048
	81–105 (n=190)	12 (6.3)	178 (93.7)	
SITS-SICH score	0–4 (n=165)	5 (3.0)	160 (97.0)	0.276
	5–15 (n=145)	8 (5.5)	137 (94.5)	
Patients with IVT+EVT				
SEDAN score	0–2 (n=142)	7 (4.9)	135 (95.1)	0.356
	3–6 (n=174)	13 (7.5)	161 (92.5)	
GRASPS score	45–80 (n=114)	5 (4.4)	109 (96.4)	0.301
	81–105 (n=205)	15 (7.3)	190 (92.7)	
SITS-SICH score	0–4 (n=158)	7 (4.4%)	151 (96.4)	0.166
	5–15 (n=158)	13 (8.3)	145 (91.7)	
EVT, endovascular thrombectomy; GRASPS, Glucose, Race, Age, Sex, systolic blood Pressure, and Severity of stroke; IVT, intravenous thrombolysis; SEDAN, blood Sugar, Early infarct signs and (hyper)Dense cerebral artery sign, Age, and National Institutes of Health Stroke Score; sICH, symptomatic intracranial hemorrhage; SITS-SICH, Safe Implementation of Thrombolysis in Stroke-Symptomatic Intracerebral Hemorrhage.				

EVT, endovascular thrombectomy; GRASPS, Glucose, Race, Age, Sex, systolic blood Pressure, and Severity of stroke; IVT, intravenous thrombolysis; SEDAN, blood Sugar, Early infarct signs and (hyper)Dense cerebral artery sign, Age, and National Institutes of Health Stroke Score; sICH, symptomatic intracranial hemorrhage; SITS-SICH, Safe Implementation of Thrombolysis in Stroke-Symptomatic Intracerebral Hemorrhage.

non-inferiority of EVT alone. The MR CLEAN-NO IV (Multi-center Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) trial failed to show superiority or non-inferiority.¹⁰ SWIFT-DIRECT (Bridging Thrombolysis vs Direct Mechanical Thrombectomy in Acute Ischemic Stroke) and DIRECT-SAFE (DIRECT Endovascular Clot Retrieval vs Standard Bridging Thrombolysis With Endovascular Clot Retrieval) did not show the non-inferiority of omitting IVT, using generous non-inferiority margins (12% and 10%).^{11 12} In an expedited guideline from the European Stroke Organisation, a study level meta-analysis of all six trials showed that a prespecified 1.3% benefit on functional independence of IVT could not be ruled out.²⁴

To separately evaluate the potentially increased ICH risk of alteplase administration before EVT, we selected three scales for assessing the risk of sICH after IVT: SEDAN, GRASPS, and SITS-SICH scores.^{16–18} Although patients with a higher score were more likely to have sICH after EVT, the prediction was not very accurate in our study, considering these scales were developed for patients with IVT alone. In this subgroup analysis, we could not confirm the hypothesis that an individual's bleeding risk modifies the effect of alteplase when applied as bridging therapy before EVT. Patients treated with EVT alone or bridging therapy had similar functional outcomes in all subgroups based

Table 2 Baseline characteristics stratified by Safe Implementation of Thrombolysis in Stroke-Symptomatic Intracerebral Hemorrhage risk score

Variables	SITS-SICH score (0–4)			SITS-SICH score (5–15)		
	EVT alone (n=165)	IVT+EVT (n=158)	P ₁	EVT alone (n=145)	IVT+EVT (n=158)	P ₂
Age (year)	65 (55–71)	65 (56–71)	0.86	75 (69–80)	75 (66–80)	0.59
Men (n (%))	103 (62.4)	95 (60.1)	0.67	74 (51.0)	83 (52.5)	0.79
Weight (kg)	66.8±10.7	65.7±11.2	0.27	65.2±12.5	63.7±11.6	0.28
Medical history						
Hypertension (n (%))	63 (38.2)	70 (44.3)	0.26	116 (80.0)	126 (79.8)	0.96
Diabetes mellitus (n (%))	16 (9.7)	20 (12.7)	0.40	37 (25.5)	47 (29.8)	0.41
Atrial fibrillation (n (%))	62 (37.6)	66 (41.8)	0.44	83 (57.2)	77 (48.7)	0.14
Prior ischemic stroke (n (%))	20 (12.1)	18 (11.4)	0.84	21 (14.5)	27 (17.1)	0.53
Smoking (n (%))	45 (27.3)	40 (25.3)	0.69	25 (17.2)	29 (18.4)	0.80
Pre-stroke mRS ≥1 (n (%))	8 (4.9)	10 (6.3)	0.44	18 (12.4)	12 (7.6)	0.12
Prior antiplatelet use (n (%))	4 (2.4)	2 (1.3)	0.72	43 (29.7)	50 (31.7)	0.71
Baseline NIHSS score	16 (11–20)	15 (12–20)	0.81	18 (15–22)	19 (15–23)	0.20
Baseline glucose (mmol/L) (mean±SD)	6.8±1.6	7.0±2.0	0.66	8.6±3.8	8.8±3.4	0.37
Onset to puncture (min) (mean±SD)	193±59	197±61	0.73	209±58	221±55	0.08
Image variables						
Hyperdense artery sign (n (%))	76 (46.6)	71 (44.9)	0.76	64 (44.4)	68 (43.6)	0.88
Early infarct sign (n (%))	103 (63.2)	108 (68.4)	0.33	107 (74.3)	100 (64.1)	0.06
ASPECTS	9 (7–10)	9 (7–10)	0.44	8 (6–10)	9 (7–10)	0.20
Collateral score (n (%))			0.60			0.50
0–1	120 (72.7)	119 (75.3)		120 (82.8)	126 (79.8)	
2–3	45 (27.3)	39 (24.7)		25 (17.2)	32 (20.3)	
Occlusion site (n (%))			0.88			0.29
ICA	51 (31.5)	54 (34.2)		58 (40.6)	56 (35.7)	
M1	93 (57.4)	87 (55.1)		65 (45.5)	85 (54.1)	
M2	18 (11.1)	17 (10.8)		20 (14.0)	15 (9.6)	

ASPECTS, Alberta Stroke Program Early CT Score; EVT, endovascular thrombectomy; ICA, internal carotid artery; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SITS-SICH, Safe Implementation of Thrombolysis in Stroke-Symptomatic Intracerebral Hemorrhage.

on the sICH risk prediction scores. There are several possible explanations: (1) the non-significantly higher hemorrhage (asymptomatic ICH or sICH) rate might offset the benefits of partial thrombi dissolution; (2) the development of sICH might mainly relate to reperfusion of brain tissue (reperfusion injury), but not the specific treatment approach (limited influence); and (3) alteplase was usually still running during the thrombectomy procedure due to the short time interval between the beginning of IVT to groin puncture in the DIRECT-MT trial, which might reduce the benefits of alteplase.

In most clinical trials, the risk of sICH did not increase significantly when alteplase was applied as adjunctive therapy before EVT. For example, there was no significant difference in the occurrence of sICH (Heidelberg definition) between the EVT alone group and the bridging therapy group in the DIRECT-MT trial (4.3% vs 6.1%),⁷ DEVT trial (6.1% vs 6.8%),⁸ and MR CLEAN-NO IV trial (5.9% vs 5.3%).¹⁰ The current study also

Table 3 Primary, secondary, and safety outcomes stratified by Safe Implementation of Thrombolysis in Stroke-Symptomatic Intracerebral Hemorrhage risk score

Outcome	SITS-SICH score (0–4)			SITS-SICH score (5–15)		
	EVT alone	IVT+EVT	Adjusted OR	EVT alone	IVT+EVT	Adjusted OR
Primary outcome						
Functional independence at 90 days (mRS 0–2) (n (%))	76 (46.0)	75 (47.5)	1.12 (0.68 to 1.82)	36 (25.0)	44 (27.9)	0.92 (0.53 to 1.60)
Secondary outcomes						
Favorable functional outcome at 90 days (mRS 0–1) (n (%))	55 (33.3)	48 (30.4)	1.45 (0.86 to 2.43)	21 (14.6)	24 (15.2)	0.95 (0.49 to 1.85)
Successful reperfusion before EVT (n (%))	5 (3.1)	10 (6.4)	0.49 (0.16 to 1.51)	3 (2.1)	13 (8.3)	0.27 (0.07 to 0.99)
Successful reperfusion after EVT (n (%))	129 (82.2)	137 (88.4)	0.59 (0.31 to 1.13)	111 (78.2)	127 (81.4)	0.72 (0.40 to 1.28)
Safety outcomes (n (%))						
Death	27 (16.4)	21 (13.3)	1.14 (0.60 to 2.18)	29 (20.1)	34 (21.5)	0.93 (0.51 to 1.69)
Symptomatic intracranial hemorrhage	5 (3.0)	7 (4.4)	0.63 (0.19 to 2.05)	8 (5.5)	13 (8.2)	0.66 (0.26 to 1.69)
Asymptomatic intracranial hemorrhage	63 (38.2)	43 (27.2)	1.56 (0.95 to 2.57)	44 (30.3)	73 (46.2)	0.53 (0.33 to 0.87)

EVT, endovascular thrombectomy; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; SITS-SICH, Safe Implementation of Thrombolysis in Stroke-Symptomatic Intracerebral Hemorrhage.

revealed that omitting IVT before EVT would not lead to better functional outcomes even in patients with a high bleeding risk, indicating that clinicians should not be overly concerned about the hemorrhagic events of bridging therapy, especially in cases of delay in EVT. On the other hand, successful reperfusion before EVT occurred more frequently in patients who received bridging therapy. Therefore, the cost efficiency of bridging therapy is evaluated, both the increased cost of alteplase use and the reduced cost due to recanalization prior to the EVT attempt should be considered.

This subgroup analysis had several limitations. First, the statistical tests for interactions between individual bleeding risk and treatment allocation may be underpowered. If the sample size allows, we could further focus on patients with an extremely high bleeding risk. Second, as mentioned above, time from IVT infusion to EVT procedure may not have been adequate to state conclusively the lack of benefit of alteplase. Third, the three scales for predicting sICH after IVT are not specific to ischemic stroke patients with large vessel occlusion.

In conclusion, there is currently no evidence that clinicians can decide whether to omit IVT before EVT based on an

individualized assessment of bleeding risk. Pooled analysis of randomized trials may provide greater clarity.

Contributors SY and MZ: conceptualization, data curation, methodology, software, and writing-original draft. HZ: Data curation, formal analysis, investigation, and writing-review and editing. YZ: data curation, formal analysis, supervision, and writing-review and editing. YC, XZ, ZC, PY, YZ, LZ, ZL, and PX: data curation, validation, and writing-review and editing. JS: conceptualization, project administration, resources, supervision, and writing-review and editing. ML: conceptualization, funding acquisition, project administration, resources, supervision, writing-review and editing. JL: conceptualization, project administration, and writing-review and editing. ML (guarantor) accepted full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish.

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Data availability statement Data are available upon reasonable request.

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Table 4 Treatment-by-bleeding-risk interactions for all dichotomized modified Rankin Scale outcomes based on the three scores

mRS score at 90 days	SEDAN score		GRASPS score		SITS-SICH score	
	Unadjusted P	Adjusted P	Unadjusted P	Adjusted P	Unadjusted P	Adjusted P
0 or 1	0.41	0.59	0.49	0.57	0.79	0.85
0–2	0.96	0.85	0.94	0.94	0.92	0.92
0–3	0.39	0.32	0.67	0.63	0.70	0.66
0–4	0.53	0.49	0.52	0.51	0.85	0.80
0–5	0.38	0.37	0.40	0.38	0.38	0.38

GRASPS, Glucose, Race, Age, Sex, systolic blood Pressure, and Severity of stroke; mRS, modified Rankin Scale; SEDAN, blood Sugar, Early infarct signs and (hyper)Dense cerebral artery sign, Age, and National Institutes of Health Stroke Score; SITS-SICH, Safe Implementation of Thrombolysis in Stroke-Symptomatic Intracerebral Hemorrhage.

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Supplemental Table 1. Baseline characteristics stratified by the SEDAN risk score

Variables	SEDAN score (0-2)		P ₁	SEDAN score (3-6)		P ₂
	EVT alone	IVT+EVT		EVT alone	IVT+EVT	
	(n=132)	(n=142)		(n=179)	(n=174)	
Age (year)	67(55-72)	68(59-73)	0.15	74(65-79)	72(62-78)	0.22
Male, %	82(62.1)	84(59.2)	0.62	95(53.1)	93(53.5)	0.94
Weight, kg	66.0±10.8	64.5±11.4	0.19	66.1±12.2	64.7±11.5	0.33
Medical history						
Hypertension, %	66(50.0)	84(59.2)	0.13	115(64.3)	112(64.4)	0.98
Diabetes mellitus, %	14(10.6)	17(12.0)	0.72	39(21.8)	50(28.7)	0.13
Atrial fibrillation, %	54(40.9)	65(45.8)	0.42	93(52.0)	79(45.4)	0.22
Prior ischemic stroke, %	18(13.6)	18(12.7)	0.82	23(12.9)	27(15.5)	0.47
Smoking, %	34(25.8)	37(26.1)	0.96	36(20.1)	31(17.8)	0.58
Pre-stroke mRS≥1, %	15(11.4)	13(9.2)	0.44	11(6.2)	10(5.8)	0.60
Prior antiplatelet use, %	19(14.4)	20(14.1)	0.94	27(15.1)	31(17.8)	0.49
Baseline NIHSS score	15(10-20)	16(12-21)	0.33	18(14-23)	19(15-23)	0.49
Baseline glucose (mmol/L)	6.5±1.2	6.7±1.6	0.90	8.6±3.5	8.8±3.3	0.38
Onset to puncture (min)	199±57	203±59	0.68	202±61	213±59	0.08
Image variables						
Hyperdense artery sign, %	25(18.9)	26(18.3)	0.89	115(64.3)	113(64.9)	0.89
Early infarct sign, %	61(46.2)	62(43.7)	0.97	152(84.9)	148(85.1)	0.97
ASPECTS	10(8-10)	10(9-10)	0.38	8(6-9)	8(6-9)	0.27
Collateral score			0.61			0.80
0-1, %	102(77.3)	106(74.7)		141(78.8)	139(79.9)	
2-3, %	30(22.7)	36(25.4)		38(21.2)	35(20.1)	
Occlusion site			0.76			0.58
ICA, %	29(22.1)	33(23.6)		82(46.3)	76(43.7)	
M1, %	79(60.3)	87(62.1)		79(44.6)	85(48.9)	
M2, %	23(17.6)	20(14.3)		16(9.0)	12(6.9)	

SEDAN: blood Sugar, Early infarct signs and [hyper]Dense cerebral artery sign, Age, and NIHSS; EVT: endovascular thrombectomy; IVT: intravenous thrombolysis; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; ASPECTS: Alberta Stroke Program Early CT Score; ICA: internal carotid artery.

Supplemental Table 2. Baseline characteristics stratified by the GRASPS risk score

Variables	GRASPS score (45-80)		P ₁	GRASPS score (81-105)		P ₂
	EVT alone	IVT+EVT		EVT alone	IVT+EVT	
	(n=124)	(n=114)		(n=190)	(n=205)	
Age (year)	63(52-69)	63(55-70)	0.40	74(67-79)	73(64-79)	0.28
Male, %	74(59.7)	61(53.5)	0.34	105(55.3)	119(58.1)	0.58
Weight, kg	66.6±11.0	65.4±10.4	0.41	65±11.9	64.2±12.0	0.17
Medical history						
Hypertension, %	57(46.0)	55(48.3)	0.73	124(65.3)	143(69.8)	0.34
Diabetes mellitus, %	15(12.1)	21(18.4)	0.17	38(20.0)	47(22.9)	0.48
Atrial fibrillation, %	49(39.5)	44(38.6)	0.88	99(52.1)	101(49.3)	0.57
Prior ischemic stroke, %	14(11.3)	12(10.5)	0.85	27(14.2)	33(16.1)	0.60
Smoking, %	33(26.6)	28(24.6)	0.72	38(20.0)	41(20.0)	1.00
Pre-stroke mRS≥1, %	13(10.5)	9(7.9)	0.44	13(6.8)	14(6.8)	0.97
Prior antiplatelet use, %	19(15.3)	11(9.7)	0.19	28(14.7)	42(20.5)	0.13
Baseline NIHSS score	12(10-15)	13(10-15)	0.47	19(16-23)	20(17-24)	0.35
Baseline glucose (mmol/L)	6.9±2.2	7.1±2.4	0.87	8.3±3.3	8.3±3.1	0.74
Onset to puncture (min)	202±58	205±62	0.93	200±60	211±58	0.07
Image variables						
Hyperdense artery sign, %	45(36.9)	44(38.9)	0.75	95(50.3)	95(46.8)	0.49
Early infarct sign, %	74(60.7)	75(66.4)	0.36	139(73.5)	135(66.5)	0.13
ASPECTS	9(7-10)	9(8-10)	0.80	8(6-10)	8(6-10)	0.62
Collateral score			0.32			0.45
0-1, %	92(74.2)	78(68.4)		152(80.0)	170(82.9)	
2-3, %	32(25.8)	36(31.6)		38(20.0)	35(17.1)	
Occlusion site			0.97			0.38
ICA, %	32(26.2)	31(27.4)		79(42.3)	79(38.9)	
M1, %	74(60.7)	68(60.2)		85(45.5)	105(51.7)	
M2, %	16(13.1)	14(12.4)		23(12.3)	18(8.9)	

GRASPS: Glucose, Race, Age, Sex, systolic blood Pressure, and Severity of stroke; EVT: endovascular thrombectomy; IVT: intravenous thrombolysis; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; ASPECTS: Alberta Stroke Program Early CT Score; ICA: internal carotid artery.

Supplemental Table 3. Primary, secondary and safety outcomes stratified by the SEDAN risk score (EVT alone versus IVT+EVT)

Outcome	SEDAN score (0-2)		Adjusted OR	SEDAN score (3-6)		Adjusted OR
	EVT alone	IVT+EVT		EVT alone	IVT+EVT	
Primary outcome						
Functional independence at 90 d (mRS 0-2), %	60(45.5)	71(50.0)	1.00(0.58-1.71)	50(28.1)	47(27.0)	1.14 (0.69-1.88)
Secondary outcomes						
Favorable functional outcome at 90 d (mRS 0-1), %	43(32.6)	50(35.2)	1.07(0.62-1.86)	31(17.4)	21(12.1)	1.54(0.83-2.86)
Successful reperfusion before EVT, %	2(1.5)	16(11.5)	0.12(0.03-0.53)	6(3.5)	6(3.5)	1.00(0.31-3.22)
Successful reperfusion after EVT, %	106(82.2)	119(86.2)	0.75(0.38-1.46)	136(78.6)	144(83.2)	0.65(0.37-1.13)
Safety outcomes						
Death, %	13(9.9)	17(12.0)	0.62(0.28-1.39)	46(25.8)	39(22.4)	1.10(0.65-1.85)
Symptomatic intracranial hemorrhage, %	3(2.3)	7(4.9)	0.46(0.12-1.83)	11(6.2)	13(7.5)	0.74(0.32-1.74)
Asymptomatic intracranial hemorrhage, %	40(30.3)	37(26.1)	1.13(0.65-1.96)	67(37.4)	79(45.4)	0.78(0.51-1.20)

SEDAN: blood Sugar, Early infarct signs and [hyper]Dense cerebral artery sign, Age, and National Institutes of Health Stroke Score; EVT: endovascular thrombectomy; IVT: intravenous thrombolysis; OR: odds ratio; mRS: modified Rankin Scale.

Supplemental Table 4. Primary, secondary and safety outcomes stratified by the GRASPS risk score (EVT alone versus IVT+EVT)

Outcome	GRASPS score (45-80)		Adjusted OR	GRASPS score (81-105)		Adjusted OR
	EVT alone	IVT+EVT		EVT alone	IVT+EVT	
Primary outcome						
Functional independence at 90 d (mRS 0-2), %	66(53.2)	62(54.4)	1.20(0.69-2.06)	46(24.3)	57(27.9)	0.88(0.54-1.43)
Secondary outcomes						
Favorable functional outcome at 90 d (mRS 0-1), %	44(35.5)	43(37.7)	1.06(0.61-1.84)	32(16.9)	29(14.2)	1.32(0.75-2.35)
Successful reperfusion before EVT, %	3(2.5)	10(8.9)	0.25(0.06-1.00)	5(2.8)	13(6.5)	0.43(0.15-1.26)
Successful reperfusion after EVT, %	97(80.2)	94(83.9)	0.63(0.32-1.26)	146(80.2)	171(85.1)	0.70(0.41-1.20)
Safety outcomes						
Death, %	12(9.7)	12(10.5)	0.76(0.32-1.82)	48(25.4)	45(22.1)	1.09(0.67-1.47)
Symptomatic intracranial hemorrhage, %	2(1.6)	5(4.4)	0.33(0.06-1.78)	12(6.3)	15(7.3)	0.85(0.38-1.88)
Asymptomatic intracranial hemorrhage, %	41(33.1)	36(31.6)	1.01(0.57-1.79)	67(35.3)	81(39.5)	0.88(0.58-1.33)

GRASPS: Glucose, Race, Age, Sex, systolic blood Pressure, and Severity of stroke; EVT: endovascular thrombectomy; IVT: intravenous thrombolysis; OR: odds ratio; mRS: modified Rankin Scale.

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Manuscript Number (if known): jnis-2022-019326

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Your Name: Zhicai Chen

Manuscript Title: Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known): jnis-2022-019326

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ICMJE DISCLOSURE FORM

Date:9/8/2022

Your Name:Jianmin Liu

Manuscript Title:Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known):jnis-2022-019326

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. “Related” means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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ICMJE DISCLOSURE FORM

Date: 9/8/2022

Your Name: Jun Sun

Manuscript Title: Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known): jnis-2022-019326

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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ICMJE DISCLOSURE FORM

Date:9/8/2022

Your Name:Lei Zhang

Manuscript Title:Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known):jnis-2022-019326

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ICMJE DISCLOSURE FORM

Date: 9/8/2022

Your Name: Min Lou

Manuscript Title: Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known): jnis-2022-019326

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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1	<input type="checkbox"/> None <div> <div>the National Natural Science Foundation of China</div> <div>81971101, 82171276</div> </div> <div> <div>the Science Technology Department of Zhejiang Province</div> <div>2018C04011</div> </div> <div>Click the tab key to add additional rows.</div>	
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2	<input checked="" type="checkbox"/> None <div> <div></div> <div></div> </div> <div> <div></div> <div></div> </div>	
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ICMJE DISCLOSURE FORM

Date: 9/8/2022

Your Name: Minmin Zhang

Manuscript Title: Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known): jnis-2022-019326

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ICMJE DISCLOSURE FORM

Date: 9/8/2022

Your Name: Pengfei Xing

Manuscript Title: Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known): jnis-2022-019326

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ICMJE DISCLOSURE FORM

Date:9/8/2022

Your Name: Pengfei Yang

Manuscript Title: Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known): jnis-2022-019326

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. “Related” means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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ICMJE DISCLOSURE FORM

Date: 9/8/2022

Your Name: Shenqiang Yan

Manuscript Title: Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known): jnis-2022-019326

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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ICMJE DISCLOSURE FORM

Date:9/8/2022

Your Name:Xuting Zhang

Manuscript Title:Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known):jnis-2022-019326

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. “Related” means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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ICMJE DISCLOSURE FORM

Date: 9/8/2022

Your Name: Yi Chen

Manuscript Title: Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known): jnis-2022-019326

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ICMJE DISCLOSURE FORM

Date:9/8/2022

Your Name:Yongwei Zhang

Manuscript Title:Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known):jnis-2022-019326

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12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None <div> <div></div> <div></div> <div></div> </div>	
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ICMJE DISCLOSURE FORM

Date: 9/8/2022

Your Name: Ying Zhou

Manuscript Title: Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known): jnis-2022-019326

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

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ICMJE DISCLOSURE FORM

Date: 9/8/2022

Your Name: Zifu Li

Manuscript Title: Effect of bleeding risk prediction on decision-making of intravenous thrombolysis before thrombectomy: a subgroup analysis of DIRECT-MT

Manuscript Number (if known): jnis-2022-019326

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