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ABSTRACT

Background A potential benefit of intravenous thrombolysis (IVT) before mechanical thrombectomy (MT) is pre-interventional reperfusion. Currently, there are few data on the occurrence of pre-interventional reperfusion in patients randomized to IVT or no IVT before MT.

Methods SWIFT DIRECT (Solitaire With the Intention For Thrombectomy Plus Intravenous t-PA vs DIRECT Solitaire Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke) was a randomized controlled trial including acute ischemic stroke IVT eligible patients being directly admitted to a comprehensive stroke center, with allocation to IVT with MT versus MT alone. The primary endpoint of this analysis was the occurrence of pre-interventional reperfusion, defined as a pre-interventional expanded Thrombolysis in Cerebral Infarction score of ≥2a. The effect of IVT and potential treatment effect heterogeneity were analyzed using logistic regression analyses.

Results Of 396 patients, pre-interventional reperfusion occurred in 20 (10.0%) patients randomized to IVT with MT, and in 7 (3.6%) patients randomized to MT alone. Receiving IVT favored the occurrence of pre-interventional reperfusion (adjusted OR 2.91, 95% CI 1.23 to 6.87). There was no IVT treatment effect heterogeneity on the occurrence of pre-interventional reperfusion with different strata of Randomization-to-Groin-Puncture time (p for interaction=0.33), although the effect tended to be stronger in patients with a Randomization-to-Groin-Puncture time >28 min (adjusted OR 4.65, 95% CI 1.16 to 18.68). There were no significant differences in rates of functional outcomes between patients with and without pre-interventional reperfusion.

Conclusion Even for patients with proximal large vessel occlusions and direct access to MT, IVT resulted in an absolute increase of 6% in rates of pre-interventional reperfusion. The influence of time strata on the occurrence of pre-interventional reperfusion should be studied further in an individual patient data meta-analysis of comparable trials.

Trial registration number clinicaltrials.gov NCT03192332.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a lack of data from randomized controlled trials on the occurrence of pre-interventional reperfusion in patients randomized to intravenous thrombolysis or no intravenous thrombolysis before mechanical thrombectomy.

WHAT THIS STUDY ADDS

⇒ This post hoc analysis from a randomized controlled trial showed that patients who received intravenous thrombolysis before mechanical thrombectomy were more likely to achieve pre-interventional reperfusion between qualifying imaging and first diagnostic angiography series, although there was no clear evidence that early pre-interventional reperfusion was associated with improved functional outcome or lower mortality rates.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Intravenous thrombolysis favoured pre-interventional reperfusion, but the clinical benefits of achieving pre-interventional appeared to be limited. Introduction of new thrombolytics, such as tenecteplase, might increase the effect size and overall patient outcome.

INTRODUCTION

A potential benefit of intravenous thrombolysis (IVT) before mechanical thrombectomy (MT) is pre-interventional reperfusion.[1] Observational studies have highlighted that IVT favors pre-interventional reperfusion, often resulting in incomplete reperfusion on the first diagnostic angiography run.[2–7] Despite incomplete reperfusion, these patients have good clinical outcomes.[8 9]

At present, there are few data on the occurrence of pre-interventional reperfusion in patients randomized to IVT or no IVT before MT,[10–15] and

observational data are heavily biased by the indications and contraindications for IVT.[16] The Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals (DIRECT-MT) was a randomized controlled trial (RCT) that evaluated the effect of MT alone versus a combined IVT+MT approach for large vessel occlusion anterior circulation strokes.[11] A recent subanalysis of this trial showed that pre-interventional reperfusion occurred more often in patients randomized to the IVT+MT arm, especially when the interval between IVT administration and groin puncture was more than half an hour.[17]

To elucidate the association between IVT, pre-interventional reperfusion, and clinical outcomes, we have performed a post-hoc analysis of the Solitaire With the Intention For Thrombectomy Plus Intravenous t-PA versus DIRECT Solitaire Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke (SWIFT DIRECT) trial.[10]

METHODS

SWIFT DIRECT

SWIFT DIRECT (clinicaltrials.gov NCT03192332) was one of six salient RCTs comparing the outcome of direct admission acute ischemic stroke patients randomized to either IVT with MT (IVT+MT) or MT alone apporach with 1:1 allocation.[10] Trial details have been described previously.[10 18] The trial was conducted in 48 stroke centers in eight countries, with 408 patients randomized during the period from November 2017 to May 2021.[10 18] All randomized patients had acute ischemic stroke with verified proximal occlusion in the anterior circulation. To be included, all patients had to be eligible to receive IVT and undergo MT within 75 min from imaging to groin puncture, or within 90 min from door to groin puncture. Random assignment into one of the two treatment arms was performed by probabilistic minimization. Full inclusion and exclusion criteria are included in online supplemental table 1. Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed during this study.

Imaging protocols

On admission, patients had to undergo CT angiography or MR angiography. Follow-up imaging was performed 24±6 hours after the intervention on a non-contrast CT and CT angiography or MRI and MR angiography. An independent central core laboratory evaluated all clinical imaging data.

Primary and secondary endpoints

Reperfusion outcome was graded on an expanded Thrombolysis in Cerebral Infarction (eTICI) scale, ranging from 0 (no reperfusion) to 3 (100% reperfusion of the target downstream territory). Grades 2a, 2b50, 2b67, and 2c correspond to 1–49%, 50–66%, 67–89%, and 90–99% reperfusion of the target downstream territory, respectively. Rating methods adhered to the guidelines outlined in a consensus paper.[19]

The primary endpoint of this post hoc study was pre-interventional reperfusion, defined as pre-interventional cross sectional eTICI (cs-eTICI) ≥2a. Methodological details for evaluating pre-interventional and post-interventional cs-eTICI were published with the SWIFT DIRECT trial.[10] In summary, pre-interventional cs-eTICI evaluates reperfusion status on the first diagnostic angiography images relative to the target downstream territory seen on qualifying cross sectional imaging (CT or MRI). If clot migration occurred from the distal M1 to the proximal M2 territory, this would correspond to a cs-eTICI 2b50 score, because approximately half of the initially occluded target territory is now perfused. Conversely, if thrombus migration occurs from the proximal to the distal M1, this would not be rated as pre-interventional cs-eTICI 2a despite potential antegrade flow occurring in the lenticulostraiate arteries, because it is methodologically imprecise to evaluate lenticulostraiate artery reperfusion due to their branching variances. More details can be found in the online supplementary appendix.

The cut-off of cs-eTICI ≥2a was chosen because of the low numbers of patients with a pre-interventional cs-eTICI score of ≥2b50 or 2b67 (n=10 and 7, respectively) and because observational evidence indicates that patients with a pre-interventional cs-eTICI score of ≥2a have favorable outcomes, suggesting an important clinical effect of this imaging endpoint.[2 17] Secondary endpoints were: complete reperfusion, defined as post-interventional eTICI 3, graded on the final angiography imaging; change in 24 hour National Institutes of Health Stroke Scale (NIHSS) after randomization; degree of disability or dependence at the 90 day follow-up visit, assessed by the modified Rankin Scale (mRS) score (shift analysis); and 90 day all cause mortality. Safety outcomes were symptomatic intracranial hemorrhage (sICH) 24 hours after randomization and any serious adverse events reported at a 90 day follow-up examination. Assessment of secondary endpoints was performed by an independent and blinded rater during either a clinical visit or a structured telephone interview.

Statistical analysis

Baseline, intervention, and outcome variables are presented as median (IQR) or number (%) and compared according to pre-interventional reperfusion using Fischer's exact test for categorical and the Mann–Whitney–Wilcoxon test for continuous variables. All reported p values are two-sided.

The effect of treatment arm allocation on pre-interventional reperfusion was analyzed using Firth logistic regression. Firth regression is a penalized maximum likelihood method that reduces small sample bias. As a sensitivity analysis, we used conventional maximum likelihood logistic regression. Interaction models were fitted to assess whether the effect of allocation to treatment arms depended on Randomization-to-Groin-Puncture time (dichotomized at median) or occlusion sites (internal carotid artery (ICA) and M1 vs more distal vessels). The effect of pre-interventional reperfusion on secondary outcomes was analyzed using ordinal (for mRS shift), linear (for changes in NIHSS), or logistic (for all cause mortality and final eTICI=3) regression models. All models were adjusted for sex and binary stratification variables: NIHSS at baseline (≤17 vs >17), age (<70 vs ≥70 years), occlusion location (M1 only vs ICA or ICA and M1 together), tandem lesions, and Alberta Stroke Program Early CT Score (ASPECTS) (4–7 vs 8–10). Unadjusted models were used for sensitivity purposes.

Due to minimal data loss, no imputation for sporadic missing values was performed. Results of regression analyses are displayed as OR or adjusted OR (aOR), with corresponding 95% CI. P values were not adjusted for multiplicity and have to be interpreted accordingly. Smaller p values were interpreted as more evidence against the null hypothesis but a significance threshold was not used. All analyses were performed in Stata v17.0, and figures were created in R v4.0.3.

RESULTS

Baseline characteristics

A total of 408 patients were randomized in the SWIFT DIRECT trial. For the present analysis, 12 patients were excluded because pre-interventional eTICI was not evaluated, leaving 396 patients in the final analysis: 200 (50.5%) were allocated to the IVT+MT arm and 196 (49.5%) to the MT only arm. In total, 27 (6.8%) patients had pre-interventional reperfusion (cs-eTICI ≥2a). Median age was 72 (64–81) years, 51.5% were women, with a median admission NIHSS score of 17 [13-20]. Both cohorts had similar baseline profiles except for some evidence that patients with pre-interventional reperfusion were more likely to have hypertension compared with patients without pre-interventional reperfusion (77.8% vs 57.2%, p=0.043) (table 1).

Pre-interventional reperfusion and treatment arm allocation

Pre-interventional reperfusion occurred in 10.0% (n=20) of patients randomized to IVT+MT, and in 3.6% (n=7) of patients randomized to MT only (OR for IVT+MT group 2.9, 95% CI 1.2 to 6.8, absolute risk difference 6.4%, 95% CI 1.4 to 11.4). This association was also strong when analyses were adjusted for stratification factors and sex (aOR for IVT+MT group 2.9, 95% CI 1.2 to 6.8), absolute risk difference 6.9%, 95% CI 1.7 to 12.2). Pre-interventional reperfusion rates stratified by eTICI score and baseline occlusion site are provided in online supplemental table 2. After pre-interventional reperfusion was achieved, 77.8% (21/27) of patients underwent further MT, while 22.2% (6/27) did not, either because of thrombus resolution or migration into distal arteries not amendable by mechanical maneuvers. All of these six patients received IVT (online supplemental table 3).

There was no interaction evidence for Randomization-to-Groin-Puncture time (p for interaction=0.33) or presence of distal vessel occlusions (p for interaction=0.47) on the effect of IVT regarding the occurrence of pre-interventional reperfusion, although the effect tended to be stronger in patients with Randomization-to-Groin-Puncture time >28 min (aOR 4.7, 95% CI 1.2 to 18.7, figure 1). Unadjusted and conventional logistic regression analyses gave comparable results (online supplemental figure 1).

There was no association between pre-interventional reperfusion rates and Onset-to-IVT time (OR 1.49, 95% CI 0.84 to 2.66 per hour delay) in patients randomized to the IVT+MT arm. Comparable point estimates were observed in a dichotomized analysis using the median time between symptom onset to administration of IVT (OR 2.10, 95% CI 0.79 to 5.61, ≥144 min). Sensitivity analyses for pre-interventional reperfusion rates with endpoints of eTICI 2b50 or eTICI 2b67 were considered low powered and extraneous due to the small number of included patients, but point estimates were comparable (online supplemental table 4).

Interventional characteristics

Patients with pre-interventional reperfusion more often did not need any mechanical devices (cs-eTICI ≥2a, 22.2% vs cs-eTICI <2a, 0%; p<0.001) and had a lower number of device passes (1 [1–2] vs 1 [1–3]; p=0.0046). Other interventional characteristics were comparable between the two groups (online supplemental table 5). We did not find any evidence that occurrence of pre-interventional reperfusion was associated with the final reperfusion outcome (cs-eTICI<2a vs cs-eTICI ≥2a: 93% vs 89%, p=0.42 for final eTICI ≥2b; 34% vs 26%, p=0.41 for final eTICI=3; table 2). Adjusted regression analysis showed an aOR of 1.4 (95% CI 0.6 to 3.4) for the effect of pre-interventional reperfusion (cs-eTICI ≥2a) on post-interventional complete reperfusion (eTICI 3, online supplemental figure 2).

Clinical outcomes

For the unadjusted analysis, there was no evidence that pre-interventional reperfusion had an effect on changes in the NIHSS rates evaluated at 24 hours after the intervention (mean difference 0.2, 95% CI −2.7 to 3.2; online supplemental figure 3), or on functional outcome at 90 days (mRS score 0–2) between patients with and without pre-interventional reperfusion (OR 1.02, 95% CI 0.5 to 2.01). Mortality at 90 days was also similar between the two groups (OR 0.5, 95% CI 0.1 to 2.7). Adjusted analyses for all secondary outcomes gave similar results (figure 2 and online supplemental figure 2). Rates of sICH at 24 hours were similar between the groups (cs-eTICI <2a, 2.7% vs cs-eTICI ≥2a, 3.7%; p=0.54), as were the rates of serious adverse events within 90 days after the index event (cs-eTICI <2a vs cs-eTICI ≥2a: 28% vs 19%; p=0.37). Rates of access site complications and sICH were also comparable between the two randomized arms (online supplemental table 6).

DISCUSSION

The main findings of this study were: (1) Patients who received IVT before MT were more likely to achieve pre-interventional reperfusion between qualifying imaging and first diagnostic angiography series compared with patients who underwent MT without IVT; (2) IVT may have a stronger effect on pre-interventional reperfusion when about half an hour has passed between its administration and groin puncture, but this trial was underpowered to show significant effect heterogeneity; (3) More than 75% of patients with pre-interventional reperfusion underwent MT for remaining vessel occlusions; (4) Early pre-interventional reperfusion was not associated with improved functional outcome at 3 months or increased rates of sICH.

IVT and pre-interventional reperfusion

Current data on the rates of pre-interventional reperfusion are heterogeneous.[1 2 6 17] A previous observational study from a prospective registry of patients with direct access to MT reported rates of 6.2% (95% CI 4.6% to 8.4%) for pre-interventional TICI ≥2a reperfusion, with IVT pretreatment being a significant predictor of pre-interventional reperfusion (aOR 11.9, 95% CI 4.5 to 31.6).[2] Reports from the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke (MR CLEAN) registry showed a change in occlusion site in 22% (302/1349) of patients, with the most common change in occlusion sites from ICA to M1 (8%, n=121).[6] This effect was significantly associated with receiving IVT (patients with IVT vs no-IVT, 25% vs 14%; p<0.001).[6] A recent post hoc analysis of the DIRECT-MT trial reported pre-interventional reperfusion rates of 15%, where IVT patients had significantly higher pre-interventional reperfusion rates compared with patients who did not receive IVT patients (IVT vs no IVT, 19% vs 10%; p=0.004).[17] In this post hoc analysis, IVT treatment effect modification on early reperfusion was reported in patients who had Randomization-to-Groin-Puncture time of >33 min (p for interaction=0.012).[17]

In our post hoc analysis, 7% patients experienced pre-interventional reperfusion, with a significantly higher occurrence in patients randomized to the IVT+MT arm, confirming previous findings on the association between IVT pretreatment and higher pre-interventional reperfusion rates.[2–7] In

Table 1 Baseline characteristics stratified by pre-interventional reperfusion

Variables	Total (n=396)		Previous cs-eTICI <2a (n=369)		Previous cs-eTICI ≥2a (n=27)		P value
	No*		No*		No*		
Treatment arm (n (%))	396		369		27		0.015
IV t-PA + MT		200 (50.5)		180 (48.8)		20 (74.1)	
MT only		196 (49.5)		189 (51.2)		7 (25.9)	
Age at inclusion (years) (median (IQR))	396	72 (64–81)	369	72 (64–81)	27	70 (62–83)	0.75
Women (n (%))	396	204 (51.5)	369	188 (50.9)	27	16 (59.3)	0.43
NIHSS (median (IQR))	396	17 (13–20)	369	17 (13–20)	27	18 (13–21)	0.67
Pre-stroke mRS (n (%))	396		369		27		0.80
0		336 (84.8)		312 (84.6)		24 (88.9)	
1		59 (14.9)		56 (15.2)		3 (11.1)	
4		1 (0.3)		1 (0.3)		0 (0.0)	
Weight (kg) (median (IQR))	371	75 (65–85)	344	75 (65–85)	27	70 (66–85)	0.96
Systolic blood pressure (mm Hg) (median (IQR))	391	147 (130–162)	364	147 (130–162)	27	147 (131–163)	0.94
Diastolic blood pressure (mm Hg) (median (IQR))	388	80 (70–90)	361	80 (70–90)	27	76 (69–89)	0.43
Heart rate (beat/min) (median (IQR))	385	74 (64–87)	359	74 (64–88)	26	75 (65–81)	0.78
Risk factors (n (%))							
Previous ischemic stroke	382	39 (9.8)	357	36 (9.8)	25	3 (11.1)	0.74
Previous transient ischemic attack	377	20 (5.1)	351	20 (5.4)	26	0 (0.0)	0.38
History of hypertension	386	232 (58.6)	359	211 (57.2)	27	21 (77.8)	0.043
History of atrial fibrillation	375	37 (9.3)	349	35 (9.5)	26	2 (7.4)	1.00
History of hypercholesterolemia	375	126 (31.8)	349	116 (31.4)	26	10 (37.0)	0.53
Previous intracerebral hemorrhage	385	2 (0.5)	359	2 (0.5)	26	0 (0.0)	1.00
Previous myocardial infarction	378	41 (10.4)	352	39 (10.6)	26	2 (7.4)	1.00
Medication (n (%))							
Warfarin or other anticoagulant	396	15 (3.8)	369	14 (3.8)	27	1 (3.7)	1.00
Aspirin	396	102 (25.8)	369	96 (26.0)	27	6 (22.2)	0.82
Statin or other lipid lowering agent	396	115 (29.0)	369	105 (28.5)	27	10 (37.0)	0.38
Laboratory values							
Blood glucose level (mmol/L) (median (IQR))	373	6.5 (5.8–7.5)	348	6.5 (5.8–7.5)	25	6.8 (6.0–7.8)	0.50
International normalized ratio (median (IQR))	309	1.0 (1.0–1.1)	290	1.0 (1.0–1.1)	19	1.1 (1.0–1.1)	0.28
Platelet count $\times 10^{e9}$(g/L) (median (IQR))	393	226 (188–272)	366	226 (187–270)	27	238 (193–319)	0.28
Hemoglobin (g/L) (median (IQR))	396	137 (125–146)	369	137 (125–146)	27	135 (118–146)	0.50
Glomerular filtration rate (mL/min) (median (IQR))	396	76 (62–90)	369	76 (62–90)	27	70 (55–87)	0.43
Baseline imaging (n (%))	396		369		27		0.38
CT		195 (49.2)		185 (50.1)		10 (37.0)	
MRI		198 (50.0)		181 (49.1)		17 (63.0)	
Both		3 (0.8)		3 (0.8)		0 (0.0)	
ASPECTS (core lab) (median (IQR))	396	8.0 (7.0–9.0)	369	8.0 (7.0–9.0)	27	8.0 (7.0–9.0)	0.94
Baseline intracranial occlusion site (n (%))	396		369		27		0.77
ICA		113 (28.5)		107 (28.9)		6 (22.2)	
ICA and M1		2 (0.5)		2 (0.5)		0 (0.0)	
M1		259 (65.4)		240 (65.0)		19 (70.4)	
M2		22 (5.6)		20 (5.4)		2 (7.4)	
Distal occlusion sites (n (%))	396		369		27		0.15
No		257 (64.9)		243 (65.9)		14 (51.9)	
Yes		139 (35.1)		126 (34.1)		13 (48.1)	
Tandem lesion (n (%))	396	63 (15.9)	369	62 (16.8)	27	1 (3.7)	0.10
Stroke etiology (n (%))	396		369		27		0.74
Large artery atherosclerosis		68 (17.2)		63 (17.1)		5 (18.5)	

Continued

Table 1 Continued

Variables	Total (n=396)		Previous cs-eTICI <2a (n=369)		Previous cs-eTICI ≥2a (n=27)		P value
Cardioembolism		149 (37.6)		137 (37.1)		12 (44.4)	
Other determined etiology		18 (4.5)		18 (4.9)		0 (0.0)	
Undetermined etiology		161 (40.7)		151 (40.9)		10 (37.0)	
Timelines							
Time from stroke onset to randomization (min) (median (IQR))	396	130 (101–170)	369	128 (100–168)	27	144 (122–181)	0.08
Time from symptom onset to start of IV t-PA (min) (median (IQR))	200	145 (112–181)	180	143 (110–176)	20	160 (130–190)	0.08
Time from arrival at emergency department to IV t-PA (min) (median (IQR))	200	55 (38–72)	180	55 (37–73)	20	61 (46–71)	0.39
Time from arrival at emergency department to groin puncture (min) (median (IQR))	396	78 (62–95)	369	76 (61–94)	27	83 (73–102)	0.08
Time from randomization to groin puncture (min) (median (IQR))	396	28 (20–39)	369	28 (20–38)	27	30 (22–46)	0.30
Time from start of intravenous alteplase to groin puncture (min) (median (IQR))	200	24 (15–35)	180	24 (15–35)	20	24 (18–40)	0.93

*Number of patients with no missing data.
ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; IV t-PA, intravenous tissue plasminogen activator; M1, proximal segment of the middle cerebral artery; M2, distal segment of the middle cerebral artery; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale.

patients with longer transfer delays to the angiography suite (Randomization-to-Groin-Puncture time ≥28 min) there was a strong association between IVT and increased pre-interventional reperfusion rates but we found no statistically significant treatment effect modification by elapsed time since IVT start. Moreover, we found no clear association between Onset-to-IVT time and increasing rates of pre-interventional reperfusion. Recent subanaylsis of SWIFT DIRECT reported similar findings where different time strata between onset and admission did not show a clear impact on overall functional and safety outcomes.[18]

The twofold decrease in reperfusion rates between our study and the DIRECT-MT post hoc analysis (7% vs 15%) might be partially attributed to different methodologies and defined thresholds of pre-interventional reperfusion which have not been described in detail for DIRECT-MT. We used a novel cs-eTICI grading system by comparing reperfusion territory on the first angiogram relative to the target downstream territory of the initial cross sectional CT or MRI imaging (see Methods), with a set threshold at cs-eTICI ≥2a. Also, slightly longer Randomization-to-Groin-Puncture time (DIRECT-MT 33 min (IQR 21–47) vs SWIFT DIRECT 28 min (IQR 20–38)) could have also given IVT more favorable conditions to express its full thrombolytic effect and facilitate pre-interventional reperfusion.[20] Regardless of differently reported pre-interventional reperfusion rates, findings from both of these RCT post hoc studies corresponds to the meta-analytic observational data which had shown that about 1 in 10 patients achieve pre-interventional reperfusion due to IVT pretreatment.[1]

Recent RCTs on intravenous tenecteplase (TNK) reported high rates of pre-interventional reperfusion.[20–22] In the Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke (EXTEND-IA TNK I) trial, restoration of blood flow >50% of the involved territory was observed more frequently in patients receiving TNK compared with alteplase (22% vs 10%, adjusted incidence ratio 2.2 (95% CI 1.1 to 4.4); p=0.03 for superiority).[21] Similar high rates of pre-interventional reperfusion rates have also been shown in the Effect of Intravenous Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke (EXTEND-IA TNK II) trial where almost 20% of patients had eTICI ≥2b50 at the initial angiogram after receiving TNK.[22]

A strong effect of TNK has also been observed in posterior circulation strokes compared with alteplase (26% vs 7%; risk ratio 4.0, 95% CI 1.3 to 12) with every fourth TNK patient having no need for further MT.[23] This difference in the effect size between TNK and alteplase on pre-interventional reperfusion rates has been hypothesized to be due to its easier administration, faster pharmacokinetics, and shorter time delays when using TNK.[20–23] Meta-analysis of three different RCTs reported an overall benefit on reperfusion rates when comparing TNK with alteplase (30% vs 15%; p=0.04).[20] Similarly, another

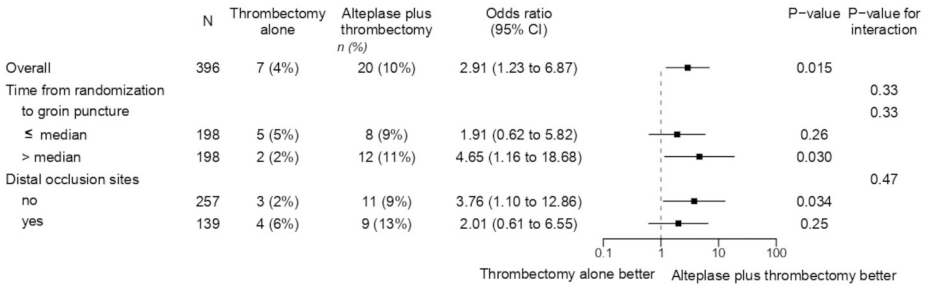

Figure 1 Odds ratio (OR) for pre-interventional reperfusion by allocation to thrombectomy alone versus alteplase plus thrombectomy. ORs are based on Firth logistic regressions adjusted for stratification factors and sex (see Methods). For subgroups, marginal effects from interaction models are presented. There was no significant interaction for Randomization-to-Groin-Puncture time (p=0.33) or presence of distal occlusions (p=0.47) on the effect of intravenous thrombolysis regarding the occurrence of pre-interventional reperfusion, although the effect tended to be stronger in patients with Randomization-to-Groin-Puncture time >28 min (adjusted OR 4.65, 95% CI 1.16 to 18.68).

Table 2 Outcome characteristics stratified by pre-interventional reperfusion

Variables	Total (n=396)	Previous cs-eTICI <2a (n=369)	Previous cs-eTICI ≥2a (n=27)	P value
Functional independence at 90 day visit (n (%))*	242 (61)	226 (61)	16 (59)	0.84
Modified Rankin Scale at 90 day visit (n (%))*				0.49
0	64 (16)	60 (16)	4 (15)	
1	98 (25)	91 (25)	7 (26)	
2	80 (20)	75 (20)	5 (19)	
3	63 (16)	58 (16)	5 (19)	
4	29 (7.3)	28 (7.6)	1 (3.7)	
5	22 (5.6)	18 (4.9)	4 (15)	
6	39 (10)	38 (10)	1 (3.7)	
Median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.94
Mortality at 90 day visit (n (%))*	39 (10)	38 (10)	1 (3.7)	0.50
Post cs-eTICI ≥2b (n (%))*	368 (93)	344 (93)	24 (89)	0.42
Post cs-eTICI=3 (n (%))*	134 (34)	127 (34)	7 (26)	0.41
Change in NIHSS at 24 hours visit (median (IQR))†	−10 (−14 to −3)	−10 (−14 to −3)	−9.0 (−13 to −3)	0.66
Any SAE within 90 days (n (%))	108 (27)	103 (28)	5 (19)	0.37
Symptomatic ICH at 24 hours visit (n (%))‡	11 (2.8)	10 (2.7)	1 (3.7)	0.54

*Data missing for one patient with previous cs-eTICI <2a.
†Data missing for 11 patients with previous cs-eTICI <2a.
‡Data missing for 5 patients with previous cs-eTICI <2a.
cs-eTICI, cross sectional expanded Thrombolysis in Cerebral Infarction; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; SAE, serious adverse events.

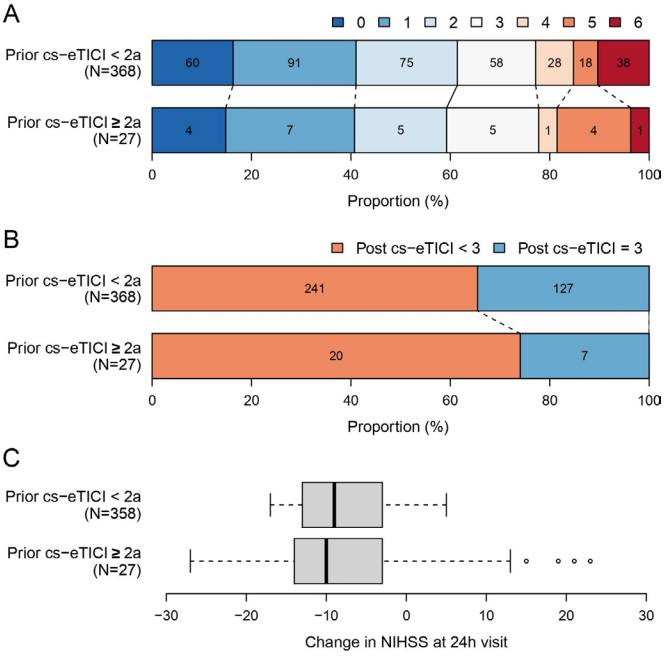

Figure 2 Effects of pre-interventional reperfusion on secondary outcomes. Secondary outcomes are mean difference or odds ratio (95% CI), based on linear ordinal logistic or logistic regression models adjusted for stratification factors and sex (see methods). Adjusted analysis on the effects of pre-interventional reperfusion showed no significant shift on the modified Rankin Scale at 3 months (adjusted OR 0.98, 95% CI 0.49 to 1.93), final eTICI 3 reperfusion (adjusted OR 1.44, 95% CI 0.61 to 3.42), and NIHSS status at 24 hours (mean difference 0.19, 95% CI −2.84 to 3.23). cs-eTICI, cross sectional expanded Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction

meta-analysis analyzed five RCTs and reported non-inferiority of TNK compared with alteplase (risk difference 4%, 95% CI −1% to 8%) when considering TNK doses of 0.25 mg/kg and 0.4 mg/kg.[24] Comparable associations were observed across other observational non-randomized studies, with reported higher odds of successful reperfusion and early neurological improvement in patients receiving TNK compared with alteplase.[25]

Because of the high rates of pre-interventional reperfusion observed after TNK, administering IV TNK over IV alteplase was endorsed by 7 of 11 experts in the ESO/ESMINT guideline committee, if vessel status is known at the time of lytic administration.[26] Currently, there is also a trial evaluating intravenous TNK+MT vs MT only (DIRECT-TNK: Randomization to Endovascular Treatment Alone or Preceded by Systemic Thrombolysis With Tenecteplase in Ischemic Stroke; clinicaltrials.gov NCT05199194), which will shed further light on the effect size of TNK concerning the rates of pre-interventional reperfusion.

Final perfusion outcome

We did not find a significant impact of pre-interventional reperfusion rates on final perfusion outcome. This finding is in contrast with other studies that have reported a negative association between pre-interventional and complete reperfusion.[2 6 17] A study from a prospective stroke registry showed that patients with pre-interventional reperfusion had lower rates of complete reperfusion compared with patients without pre-interventional reperfusion (17.9% vs 41.8%, respectively; p<0.001).[2] The MR CLEAN investigators revealed pre-interventional reperfusion to be associated with lower chances of both complete (TICI 3: aOR 0.51, 95% CI 0.36 to 0.73) and successful reperfusion (TICI 2b: aOR 0.74, 95% CI 0.55 to 0.99).[6] A post hoc analysis of the DIRECT MT showed significantly lower rates of complete final reperfusion when comparing patients who had achieved pre-interventional reperfusion to those who had not (20% vs 35%, respectively for eTICI 3 rates; p=0.008).[17]

Our findings may be explained by including patients with proximal occlusion only. Hence incomplete reperfusion due to pre-interventionel reperfusion often resulted in the clot location still being amendable to mechanical maneuvers.[10] Moreover, we found that pre-interventional reperfusion occurred more often in proximal vessels, so even if there was a pre-interventional reperfusion in the ICA or proximal M1 territory, thrombus would be dislodged in a distal M1 or proximal M2 territory, which still presents an amendable thrombectomy target. Other studies reported a higher occurrence of pre-interventional reperfusion in distal vessels.[2 6 17] Accordingly, most patients with pre-interventional reperfusion received additional mechanical interventions, which could have further increased the final reperfusion grade.

Clinical outcome

Despite higher pre-interventional reperfusion rates observed in the IVT+MT arm across the eTICI spectrum, we did not find an association between pre-interventional reperfusion and increased rates of favorable patient outcome. A partial explanation could be thrombus fragmentation by IVT which could lead from mechanically amendable proximal vessel occlusion to multiple distal vessel occlusions and worse outcome.[27] However, this scenario would be unlikely as better outcome has been consistently shown in patients with secondary distal vessel occlusions,[28] and pre-interventional reperfusion was consistently associated with better outcome despite low rates of complete reperfusion.[4–6 17] A more plausible explanation for this finding would be found in different thresholds used for defining pre-interventional reperfusion. Several analyses defined TICI 2b or 3 as a threshold for early successful pre-interventional reperfusion,[5 6] and another study rated pre-interventional reperfusion on an original thrombus migration grading scale.[4] A recent post hoc analysis of DIRECT-MT used a comparable (but not described in detail) threshold (eTICI ≥2a) for identifying pre-interventional reperfusion as our study. In this study, an independent association between pre-interventional reperfusion rates and good 3 month outcome was found.[17]

Patients with pre-interventional reperfusion in our study had tendencies towards a longer Onset-to-Randomization time compared with those without pre-interventional reperfusion, implying that some irreversible ischemic changes might have already occurred before randomization began, as the effects of early reperfusion on good clinical outcome are mainly due to shorter ischemia duration.[4–6 17] A history of hypertension was more often remarked in patients with pre-interventional reperfusion, which could have also impacted overall patient outcome and might have implications in the pathogenesis of migration and fragmentation.[29 30] Positive effects of pre-interventional reperfusion on clinical outcome reported by other studies[4–6 17] could have been counterpoised by higher hypertension rates in our cohort, as the relationship between high blood pressure and stroke outcome has been previously described.[30]

Limitations

This study had several limitations. This was a post hoc analysis and as such is subject to all of the limitations commonly ascribed to post hoc analyses. The number of patients with early reperfusion was relatively low and our analyses would most likely be underpowered to assess the true effect of pre-interventional reperfusion on clinical and functional outcome. Several patients were excluded due to missing information on pre-interventional eTICI which could have impacted the overall results. We dichotomized our time metric values and this might have resulted in some information loss. Lastly, it has also been suggested that better collateral flow might be correlated with good outcome[17] but we did not collect information on collateral status.

CONCLUSION

Even for patients with proximal large vessel occlusion with direct access to MT, IVT increases the rates of pre-interventional reperfusion by 6%. The influence of time strata on the occurrence of pre-interventional reperfusion should be further studied in an individual patient data meta-analysis of comparable trials.

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