SUPPLEMENT MATERIAL

Association of intravenous thrombolysis and pre-interventional reperfusion:

a post-hoc analysis of the SWIFT DIRECT trial

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Supplementary Methods 1 Cross-sectional eTICI

Early reperfusion before start of thrombectomy was rated using a novel, cross-sectional eTICI (cs-eTICI) score. In this grading system, the target downstream territory is defined based on findings on qualifying cross-sectional computed tomography angiography (CTA) or magnetic resonance angiography (MRA) and the amount of this territory that is reperfused is defined based on subsequent digital subtraction angiography. Pre-interventional reperfusion is assessed by comparing findings between the initial CTA/MRA and the initial digital subtraction angiography performed prior to thrombectomy. Post-intervention reperfusion is assessed by comparing findings between the initial CTA/MRA and the final digital subtraction angiography performed at the end of thrombectomy. For pre-interventional assessment, if a patient presents with a proximal M1 occlusion on admission imaging and first pre-interventional digital subtraction angiography runs show evidence of thrombus migration into a proximal M2 branch supplying 40% of the initially compromised target downstream territory, indicating reperfusion of 60%, the pre-interventional cs-eTICI score is graded as cs-eTICI2b50 (reperfusion of more than 50% of the admission target downstream territory). The proximal M2 branch then constitutes the interventional target for thrombectomy. If this can be partially recanalized (e.g., 55% of the M2 branch target downstream territory) the eTICI grade comparing pre- and post-intervention digital subtraction angiography is 2b50. In addition, the post-interventional cs-eTICI will then be cs-eTICI 2b67, reflecting the cumulative degree of reperfusion achieved when the pre-interventional and intra-interventional periods are combined. In this example, the post-interventional cs-eTICI score is derived based on:

- Pre-interventional reperfusion of 60% of the admission target downstream territory due to spontaneous or intravenous alteplase-induced thrombus dislocation/lysis.
- Post-interventional additional 55% reperfusion of the proximal M2 target downstream territory.
- The degree of reperfusion relative to the initial CTA/MRA target downstream territory achieved is 60% + (55% × 40%) = 60% + 22% + 27% of the = 82%, graded as cs-eTICI2b67 (between 67% and 90% reperfusion).

Supplementary Table 1 Full inclusion and exclusion criteria of the SWIFT DIRECT study

Inclusion criteria	**Exclusion criteria**
Informed consent as documented by signature	Acute intracranial hemorrhage
Age ≥ 18 years	Any contraindication for IV t-PA
Clinical signs consistent with an acute ischemic stroke	Pre-treatment with IV t-PA
Neurological deficit with a National Institutes of Health Stroke Scale score of ≥ 5 and < 30 (deficits judged to be clearly disabling at presentation)	In-hospital stroke
Patient is eligible for IV t-PA	Pregnancy or lactation. A negative pregnancy test before randomization is required for all women with child-bearing potential.
Patient is eligible for endovascular thrombectomy	Known (serious) sensitivity to radiographic contrast agents, nickel, titanium metals or their alloys
Randomization no later than 4 hours 15 minutes after stroke symptom onset and initiation of IV t-PA must be started within 4 hours and 30 minutes of stroke symptoms onset (onset time is measured from the time when the subject was last seen well)	Known current participation in a clinical trial
Occlusion (modified treatment in cerebral infarction [mTICI] 0–1) of the intracranial ICA, the M1 segment of the MCA, or both confirmed by computed tomography (CT) or magnetic resonance angiography, accessible for MT	Renal insufficiency as defined by a serum creatinine > 2.0 mg/dl (or 176.8 µmol/l) or glomerular filtration rate (GFR) < 30 mL/min and/or known history of renal insufficiency or requirement for hemodialysis or peritoneal dialysis
Core-infarct volume of Alberta Stroke Programme Early CT Score (ASPECTS) greater than or equal to 4 (≥ 4) based on baseline CT or MRI (a region has to have a diffusion abnormality in 20% or more of its volume to be considered MR ASPECTS positive)	Severe comorbid condition with life expectancy less than 90 days at baseline
	Known advanced dementia or significant pre-stroke disability (modified Rankin scale score ≥ 2)
	Foreseeable difficulties in follow-up due to geographic reasons (e.g. patients living abroad)
	Comorbid disease or condition that would confound the neurological and functional evaluations or compromise survival or ability to complete follow-up assessments.
	Subject currently uses or has a recent history of illicit drug(s) or abuses alcohol (defined as regular or daily consumption of more than four alcoholic drinks per day). Known history of arterial tortuosity, pre-existing stent, other arterial disease and/or known disease at the femoral access site that would prevent the device from reaching the target vessel and/or preclude safe recovery after MT
	Radiologically confirmed evidence of mass effect or intracranial tumor (except small meningioma)
	Radiologically confirmed evidence of cerebral vasculitis
	CTA or MRI evidence of carotid dissection
	Evidence of additional distal intracranial vessel occlusion in another territory (i.e. A2 segment of anterior cerebral artery or M3, M4 segment of MCA) on initial non-contrast computed tomography/MRI or CTA/MRI

IV t-PA: intravenous tissue-type plasminogen activator; MT: mechanical thrombectomy; ICA: internal carotid artery; MCA: middle cerebral artery; CT: computed tomography; MRI: magnetic resonance angiography; CTA: computed tomography angiography.

Supplementary Table 2 Pre-interventional reperfusion rates stratified by eTICI score and occlusion site

Baseline eTICI	**MT (n=196)**	**IV-tPA+MT (n=200)**	**Total (n=396)**
2a	5 (2%)	12 (6%)	17 (0.5%)
2b50	1 (0.5%)	2 (1%)	3 (0.7%)
2b67	1 (0.5%)	5 (2%)	6 (1.5%)
3	0 (0%)	1 (0.5%)	1 (0.2%)
Total	7 (3.51/%)	20 (10%)	27 (6.8%)
Baseline occlusion site	**MT (n=196)**	**IV-tPA+MT (n=200)**	**Total (n=396)**
Distal ICA - I	1 (0.5%)	0 (2%)	1 (0.2%)
Distal ICA - L	1 (0.5%)	1 (0.5%)	2 (0.5%)
Distal ICA - T	0 (0%)	3 (1.5%)	3 (0.7%)
Proximal MCA - M1	1 (0.5%)	7 (3.5%)	8 (2%)
Distal MCA - M1	3 (1.5%)	8 (4%)	11 (2.8%)
Proximal MCA - M2	1 (0.5%)	1 (0.5%)	2 (0.5%)
Total	7 (3.5%)	20 (10%)	27 (6.8%)

eTICI: expanded Treatment In Cerebral Infarction; MT: mechanical thrombectomy; IV-tPA: intravenous thrombolysis; ICA: internal carotid artery; MCA: middle cerebral artery.

Supplementary Table 3 Reasons for not performing additional mechanical thrombectomy after achieving pre-interventional reperfusion

Case	Reason for not performing MT	Group	Total IV-tPA dose given (mg)
1	During thrombectomy right MCA recanalized 30 minutes after IV-tPA	IV-tPA and MT	48
2	Thrombus has fragmented and passed into an M3 segment of the MCA (precentral branch)	IV-tPA and MT	63
3	Complete recanalization after IV-tPA	IV-tPA and MT	86
4	After carotid puncture there was no longer an M1 occlusion, intra-arterial thrombolysis performed without aspiration	IV-tPA and MT	68
5	Thrombus migration after IV-tPA with no indication for MT	IV-tPA and MT	106
6	TICI2b reperfusion after IV-tPA with residual occlusion too distal for MT	IV-tPA and MT	72

MT: mechanical thrombectomy; MCA: middle cerebral artery; IV-tPA: intravenous thrombolysis;

Supplementary Table 4 Sensitivity analyses for pre-interventional reperfusion rates with endpoints of eTICI 2b50 or eTICI 2b67

Pre-interventional reperfusion endpoint	Total number of patients (n=396)	MT (n=196)	IV-tPA+MT (n=200)	aOR for IV-tPA+MT vs MT group
eTICI 2b50	10 (2.5%)	2 (1.0%)	8 (4.0%)	3.50 (95% CI 0.84-14.57, p=0.09)
eTICI 2b67	7 (1.7%)	1 (0.5%)	6 (3.0%)	4.53 (95% CI 0.76-27.12, p=0.10)

eTICI: expanded Treatment In Cerebral Infarction; MT: mechanical thrombectomy; IVT: intravenous thrombolysis; ICA: internal carotid artery; MCA: middle cerebral artery.

Supplementary Table 5 Interventional characteristics stratified by pre-interventional reperfusion

Variables	**Total (N = 396)**	**Prior cs-eTICI < 2a (N = 369)**	**Prior cs-eTICI >= 2a (N = 27)**	**P-value**
Number of passes - median (IQR)	1.0 (1.0, 2.5)	1.0 (1.0, 3.0)	1.0 (1.0, 2.0)	0.046
Any mechanical device used - no. (%)	390 (98.5%)	369 (100.0%)	21 (77.8%)	<0.001
Balloon guide catheter used - no. (%)*	179 (45.3%)	167 (45.4%)	12 (44.4%)	1.00
Distal aspiration catheter used - no. (%)*	304 (77.0%)	287 (78.0%)	17 (63.0%)	0.10
Extracranial Stenting - no. (%)*	37 (9.4%)	36 (9.8%)	1 (3.7%)	0.49
Peri-Interventional Aspirin - no. (%)†	42 (10.7%)	41 (11.2%)	1 (3.7%)	0.34
Further thrombectomy device used after Solitaire - no. (%)	119 (30.1%)	108 (29.3%)	11 (40.7%)	0.28
Conscious sedation - no. (%)	203 (51.3%)	188 (50.9%)	15 (55.6%)	0.69
General anesthesia - no. (%)	170 (42.9%)	160 (43.4%)	10 (37.0%)	0.55
Reason for general anesthesia - no. (%)				1.00
Hospital standard practice	128 (75.3%)	120 (75.0%)	8 (80.0%)	
Clinically indicated	42 (24.7%)	40 (25.0%)	2 (20.0%)	

* Data missing for one patient with prior cs-eTICI < 2a.

† Data missing for 2 patients with prior cs-eTICI < 2a.

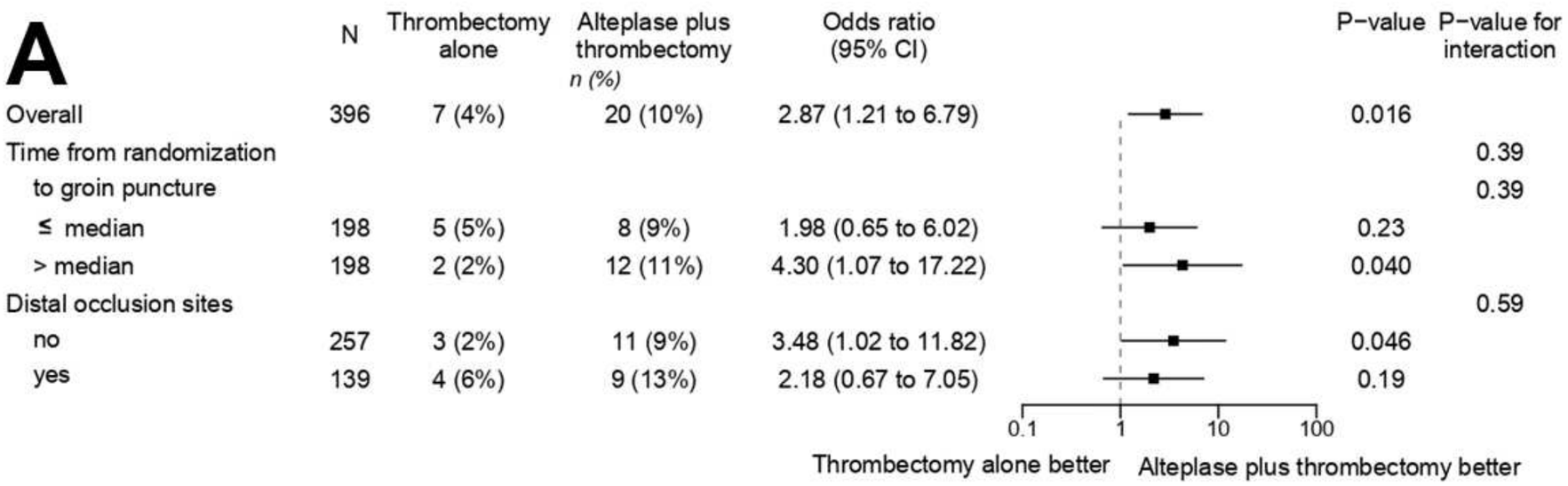
Supplementary Table 6 Rates of access site complications and sICH

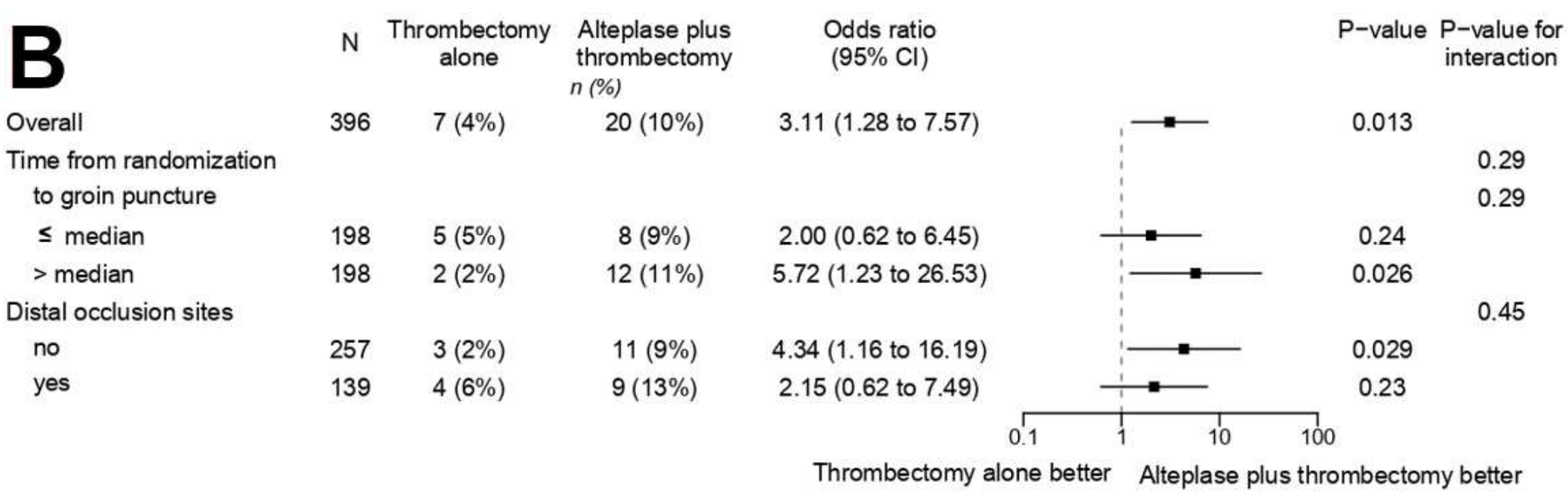
Complication	Total (n=396)	MT (n=196)	IV-tPA+MT (n=200)	p-value
Symptomatic intracerebral hemorrhage (global)*	11 (2.8%)	5 (2.6%)	6 (3.1%)	0.77
Symptomatic intracerebral hemorrhage (site) †	12 (3.1%)	3 (1.5%)	9 (4.6%)	0.14
Access site complications				
Hematoma and hemorrhage at puncture site	9 (2.3%)	2 (1.0%)	7 (3.5%)	0.27
Aneursyma spurium at puncture site	3 (0.8%)	1 (0.5%)	2 (1.0%)	1
Patients with either one complication	10 (2.5%)	3 (1.5%)	7 (3.5%)	0.34

* Data missing for 5 patients in the IV-tPA+MT arm.
† Data missing for 3 patients in the IV-tPA+MT arm.

MT: mechanical thrombectomy; IV-tPA: intravenous thrombolysis.

Supplementary Figure 1 Odds ratio for pre-interventional reperfusion by allocation to alteplase plus thrombectomy vs thrombectomy alone

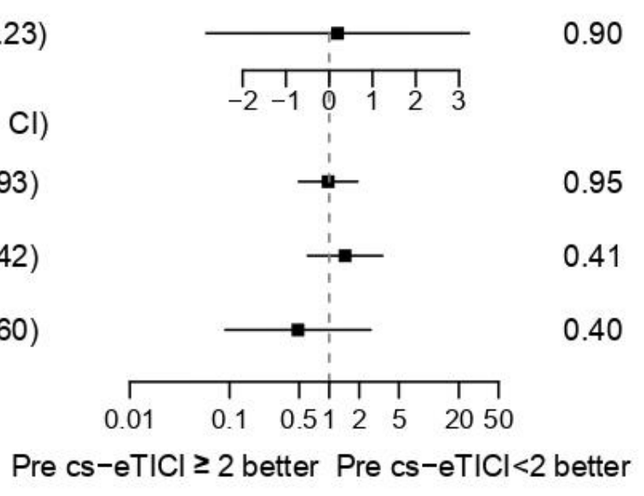




(A) Unadjusted Firth logistic regressions and (B) Conventional maximum likelihood logistic regressions adjusted for stratification factors and sex (see Methods). For subgroups, marginal effects from interaction models are presented.

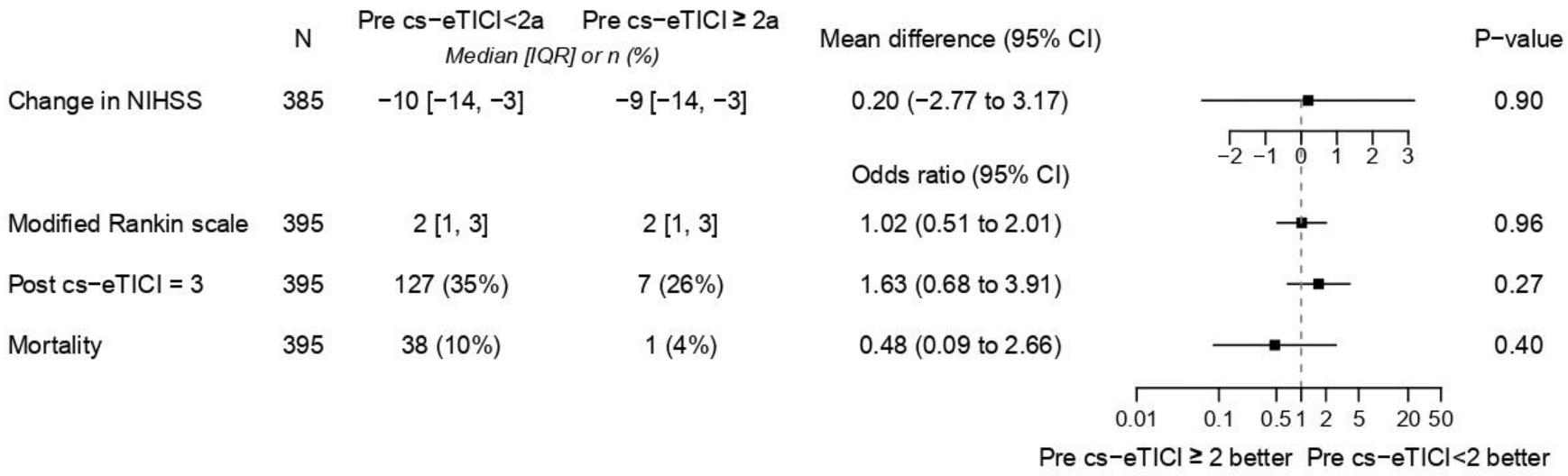
Supplementary Figure 2 Adjusted effect of pre-interventional reperfusion on secondary outcomes

	N	Pre cs−eTICI<2a	Pre cs−eTICI ≥ 2a	Mean difference (95% CI)	P−value
		Median [IQR] or n (%)			
Change in NIHSS	385	−10 [−14, −3]	−9 [−14, −3]	0.19 (−2.84 to 3.23)	0.90
				Odds ratio (95% CI)	
Modified Rankin scale	395	2 [1, 3]	2 [1, 3]	0.98 (0.49 to 1.93)	0.95
Post cs−eTICI = 3	395	127 (35%)	7 (26%)	1.44 (0.61 to 3.42)	0.41
Mortality	395	38 (10%)	1 (4%)	0.49 (0.09 to 2.60)	0.40



Mean difference or odds ratio with 95% confidence interval (CI) are plotted, based on linear, ordinal or logistic regression models (see Methods).

Supplementary Figure 3 Unadjusted effect of pre-interventional reperfusion on secondary outcomes



Presented results are a mean difference or odds ratio with 95% confidence interval (CI), based on linear, ordinal or logistic regression models. There were no significant changes in the NIHSS rates evaluated at 24 hours after the intervention (mean difference 0.20 [95% CI -2.77, 3.17]), as there was no significant shift in the modified Rankin scale score OR 1.02 [95% CI 0.51 – 2.01]). Mortality at 90 days was also similar between the groups (OR 0.48 [95% CI 0.09 – 2.66]).