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Interaction between intravenous thrombolysis and clinical outcome between slow and fast progressors undergoing mechanical thrombectomy: a post-hoc analysis of the SWIFT DIRECT trial

Running title: *Slow versus fast stroke progressors*

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- Supplemental tables: 2
- Supplemental figures: 8
- Appendix: SWIFT-DIRECT investigators list

Ethical approval disclosure statement:

The study was approved by the Cantonal Research Ethics Committee: project number 2017-00974.

Written informed consent was obtained by patients or next of kin, with selected countries allowing delayed informed consent due to emergency circumstances.

Contributorship statement:

We attest that all authors have read and approved the submitted manuscript. All authors have made substantial contributions and have approved the final submitted version. GM, JK, LB, JG, UF acquired the data, analyzed the results, drafted the manuscript and critically reviewed the manuscript. GM, LB, JK and UF performed statistical analysis and analyzed the results. IS, SS, RP, HH, PM, MM, ZK, KJ, PM, AP, JCG, MHP, LUK, GT and DL acquired the data and critically reviewed the manuscript.

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The authors declare no conflict of interest related to the present study.

ABSTRACT:

Background – In proximal occlusions, the effect of reperfusion therapies may differ between slow or fast progressors. We investigated the effect of intravenous alteplase(IVT) plus thrombectomy(MT) versus thrombectomy alone among slow versus fast stroke progressors.

Methods - The SWIFT-DIRECT trial data were analysed: 408 patients randomized to IVT+MT or MT alone. Infarct growth speed was defined by the number of point decay in initial ASPECTS divided by the onset-to-imaging time. The primary endpoint was the 3-month functional independence (modified Rankin scale 0-2). In the primary analysis, the study population was dichotomized in slow and fast progressors using median infarct growth velocity. Secondary analysis was also conducted using quartiles of ASPECTS decay.

Results - We included 376 patients[191 IVT+MT,185 MT alone; median age 73(IQR=65-81); median initial NIHSS 17(IQR=13-20)]. The median infarct growth velocity was 1.2 point/hour. Overall, we did not observe a significant interaction between the infarct growth speed and the allocation to either randomization group on the odds of favourable outcome(p=0.68). In the IVT+MT group, odds of any ICH were significantly lower in slow progressors(22.8 vs 36.4%;OR=0.52,95%CI 0.27-0.98) and higher among fast progressors(49.4 vs 26.8%;OR=2.62,95%CI 1.42-4.82)(p-value for interaction<0.001). Similar results were observed in secondary analyses.

Conclusion - In this SWIFT-DIRECT subanalysis, we did not find evidence for a significant interaction of the velocity of infarct growth on the odds of favourable outcome according to treatment by MT alone or combined IVT+MT. However, prior IVT was associated with significantly reduced occurrence of any ICH among slow progressors whereas increased in fast progressors.

KEY MESSAGES:

- What is already known on this topic:

In the setting of acute ischemic stroke due to large vessel occlusions, the velocity of infarct growth has already been demonstrated to influence clinical outcome. Patients are usually classified in slow and fast progressors. Also fast progressors has already been found to experience worse outcome after mechanical thrombectomy (MT) than slow progressors, the influence of intravenous thrombolysis (IVT) according to infarct growth pattern has been poorly investigated to date.

- What this study adds:

Despite no influence was statistically detected regarding functional outcome after 3 months, we observed that, in patients treated with IVT + MT, odds of intracranial hemorrhage (ICH) were significantly increased in fast progressors whereas significantly lower in slow progressors. In the whole study population, fast progressors were at significantly higher risk of symptomatic ICH.

- How this study might affect research, practice or policy:

Our results suggest that the fast progressor pattern of infarct growth could be associated with an increased risk of ICH. In regards with these results, prior IVT might be cautiously weighted in fast progressors intended for MT. A close monitoring of other factors increasing the ICH risk is also advised in such patients. Future therapy should target ICH, especially in patients deemed at high risk of developing such complication.

NON-STANDARD ABBREVIATIONS:

ASPECTS: Alberta Stroke Program Early Computed Tomography Score

CT: Computed Tomography

ECASS: European Cooperative Acute Stroke Study

HI: Hemorrhagic Infarction

ICH: Intracranial Hemorrhage

IQR: Interquartile range

IVH: Intraventricular hemorrhage

IVT: Intravenous Thrombolysis

MR: Magnetic Resonance

MT: Mechanical Thrombectomy

mTICI: modified Thrombolysis in Cerebral Infarction

mRS: modified Rankin Score

NIHSS: National Institute of Health Stroke Scale

PH: Parenchymal hemorrhage

RH: Remote intracranial hemorrhage

SAH: Subarachnoid hemorrhage

sICH: symptomatic intracranial hemorrhage

INTRODUCTION:

Since publication of major randomized trials regarding emergent reperfusion therapies [intravenous thrombolysis (IVT) and thrombectomy (MT)] for acute large vessel occlusion strokes, efforts are made to broaden and better determine patients who would benefit from these approaches[1,2]. Rather than standardized indications based on strict timeframe and occlusion topography, the treatment algorithm might be personalized and adapted to individual features. In this context, infarct growth speed may be a key element potentially allowing to classify patients as slow or fast progressors[3]. The ischemic progression velocity has previously been reported as an important prognostic factor that is very closely related to neuronal loss[4]. The speed of infarct growth is usually quantified using baseline imaging. Various definitions have been used to determine the infarct growth velocity and to classify patients as slow or fast progressors. Among the available literature, quickness of ischemic core extension has previously been measured using either absolute volume or Alberta Stroke Program Early CT Score (ASPECTS) on non-contrast computed tomography (CT), diffusion weighted imaging or perfusion imaging[4–12]. Initial infarct core volume should then be referred to time from onset to imaging in order to appreciate the velocity of ischemic constitution.

Among these slow and fast progressors subtypes, the effect of acute reperfusion therapies including IVT and MT may differ. Previous publications reported differences in the effect of MT according the rate of progression of the ischemic lesion[5,8,12,13]. In particular, fast progressors demonstrated worse outcome after MT than slow progressors[8,12]. Also, MT has been significantly associated to a reduced infarct growth among fast progressors[5]. On the other hand, despite evidence that IVT might be administrated cautiously in patients with low initial ASPECTS, the influence of pretreatment with IVT in the acute reperfusion strategy has never been specifically evaluated among slow and fast progressor patterns[13,14]. In the setting of endovascular treatment, the effect of IVT combined with thrombectomy compared to thrombectomy alone according the early infarct growth profile remains unknown. In this study,

we aimed to investigate the influence of allocation to either IVT+MT or MT groups of the SWIFT-DIRECT trial among patients with slow and fast stroke progression.

METHODS:

Reporting, data sharing, ethics:

For this post-hoc subanalysis of the randomized controlled SWIFT-DIRECT (https://clinicaltrials.gov/NCT03192332) study, we followed the CONSORT guidelines. The SWIFT-DIRECT dataset is not publicly available. De-identified data, together with a data dictionary will be made accessible after ethics clearance and reasonable request with a research plan to urs.fischer@usb.ch. Written informed consent was obtained by patients or next of kin, with selected countries allowing delayed informed consent due to emergency circumstances. Approval was obtained from all relevant local ethics committees.

Study population:

SWIFT-DIRECT was an international, multicenter, randomized, open label, blinded endpoint (PROBE) trial assessing the non-inferiority of MT alone versus IVT+MT in patients presenting directly to one of 48 participating MT-capable stroke centers in Europe and Canada. The trial protocol and main results, including details of the methodology, have already been published[15]. Patients were eligible if they 1) had imaging-confirmed occlusion of the intracranial carotid artery and/or the first segment (M1) of the middle cerebral artery; 2) were eligible to receive alteplase within 4.5 hours after they were last seen well; 3) could undergo MT within 75 min of randomization; and 4) had severe neurological deficits, defined as a National Institutes of Health Stroke Scale (NIHSS) score of ≥ 5. Exclusion criteria for the trial were: advanced dementia, significant pre-existing disabilities, and early extended infarct core (ASPECTS < 5). A total of 408 patients fulfilling those criteria were randomized (1:1 ratio) to undergo MT alone or IVT+MT (intravenous alteplase, 0.9 mg/kg of body weight). Among this global trial study population, patients with missing initial ASPECTS or missing time of onset or time of imaging were excluded from the present ancillary analysis.

Imaging and infarct growth velocity definition:

At the discretion of each participating center, initial imaging was performed with CT or magnetic resonance (MR) including respectively CT and MR angiography. Perfusion imaging was not mandatory in the trial protocol. An independent central core lab blinded to randomization arm and outcome evaluated all imaging data. Early infarct core progression was quantified according to the infarct volume (admission ASPECTS) on initial imaging and the onset to imaging delay. The velocity of infarct growth was calculated as 10 minus the baseline ASPECTS divided by the onset to imaging delay. The infarct growth speed is presented in ASPECTS point decay per hour (pt/h). The ASPECTS decay speed was categorized into stroke progressor groups using the median (two groups) or the quartiles (four groups).

Collected data and study outcomes:

Clinical, imaging, timeline, angiographic and follow-up data were recorded, as previously presented in the trial protocol[15]. In this sub-analysis, the primary study endpoint was functional independence, defined as a modified Rankin score (mRS) from 0 to 2, after 3 months. Secondary endpoints included efficacy endpoints: mRS at the 90-day visit, early neurological status (change in NIHSS at day 1) and successful recanalization [defined as a final modified Thrombolysis in Cerebral Infarction (mTICI) 2b, 2c or 3 at the end of the endovascular procedure]. Safety secondary endpoints were also analyzed: mortality at the 90 visit and intracranial hemorrhage (ICH) occurrence. Several ICH endpoints were defined using the ECASS-II classification. Any ICH was defined the detection of any intracranial hemorrhage on day 1 imaging of any ECASS-II subtypes including hemorrhagic infarction type 1 (HI-1), HI-2, parenchymal hemorrhage type 1 (PH-1), PH-2, subarachnoid hemorrhage (SAH), remote intracranial hemorrhage (RH) and intraventricular hemorrhage (IVH). Symptomatic ICH (sICH) was defined as an increase of the NIHSS of 4 or more compared to baseline along with the occurrence of PH-1, PH-2, SAH, RH or IVH. Asymptomatic ICH (aICH) recorded all PH-1, PH-2, SAH, RH and IVH, either associated with a NIHSS worsening or not.

Statistical analysis:

Baseline characteristics are presented as median and quartiles or absolute and relative frequencies for continuous and categorical data, respectively. Continuous data was compared between groups using the Wilcoxon-Mann-Whitney test (two groups) or the Kruskal-Wallis test (more than two groups), categorical data using Fisher's exact test.

The effect of allocation to IVT+MT vs MT alone by stroke progression was analyzed in regression models with treatment allocation, stroke progression and their interaction as covariates together with sex and the binary stratification variables from randomization, NIHSS at baseline (≤ 17 versus > 17), age (< 70 versus, ≥ 70 years), occlusion location (M1 only versus Intracranial ICA or Intracranial ICA and M1) and ASPECTS (4-7 versus 8-10). The main analysis was based on the dichotomized stroke progressor group and the secondary analysis on the four groups. Binary outcomes (functional independence, successful recanalization, mortality and ICH) were analyzed using Firth logistic regression (a penalized maximum likelihood method that reduces small-sample bias), the mRS using ordinal logistic regression and the change in NIHSS using linear regression including the baseline NIHSS and robust standard errors. We report marginal odds ratios or mean differences for each stroke progressor group with 95% confidence interval (CI) and a p-value for interaction from the Wald-test of the interaction term(s). We also performed a sensitivity analyses using "corrected ASPECTS", for which an additional point was added if the imaging modality was MRI (for ASPECTS < 10) to compensate DWI superiority in early ischemic changes detection (ref SAMURAI). The corrected decay was calculated as specified above. Three patients with both imaging modality were excluded.

The main effect of stroke progression was analyzed in the same regression models with stroke progression as covariate, adjusted for sex and the binary stratification variables from randomization. Effects are reported as marginal odds ratios or mean differences vs the slowest group for categorical progression.

Only the available data were used. Patients who died were assigned an mRS of 6 and a NIHSS of 42. The number of non-missing observations is presented. Analyses were done in Stata version 17.0, figures were drawn with R version 4.0.3 (2020-10-10).

RESULTS:

Study population:

Between November 2017 and May 2021, 408 patients were included in the SWIFT-DIRECT trial: 201 were randomized in the MT alone arm and 207 in the IVT+MT arm. In the present ancillary analysis, after exclusion of 32 patients [missing ASPECTS (n=1) and missing imaging time (n=32)], 376 were finally included. For the primary analysis, median of the ASPECTS decay was 1.2 pt/h, dichotomizing the overall study population in two groups: slow progressors (n=189) presenting with infarct growth velocity <1.2 pt/h and fast progressors (n=187) presenting infarct growth velocity >1.2 pt/h. In the secondary analysis, quartiles of ASPECTS decay were categorized as follow, from slower to faster progressors: <0.7 pt/h, 0.7 to 1.2 pt/h, 1.2 to 1.8 pt/h and >1.8 pt/h. Baseline and procedural characteristics of the global study population and of the slow and fast progressors subgroups are presented in **Table 1** and **Table 2**. Slow and fast progressors subgroups were globally balanced, especially regarding the allocation to IVT+MT or MT alone arms. However, slow progressors were older (median age 75 vs 71, p=0.004), presented less frequently with a history of hypertension (57.6 vs 67.6%, p=0.05), presented lower initial NIHSS (median NIHSS 16 vs 18, p<0.001), higher baseline ASPECTS (median 9 vs 7, p<0.001), longer delay from symptoms onset to randomization (142 minutes vs 117, p<0.001) and were less frequently treated under general anesthesia (36.5% vs 53.5%, p<0.001).

Interaction between infarct growth velocity and type of reperfusion therapy:

In the primary analysis, we did not find evidence for heterogeneity in the odds of functional independence or better outcome on the mRS among slow and fast progressors according to the allocation to either IVT+MT or MT alone groups (p-values for interaction = 0.68 and 0.22)

(see **Figures 1** & **2**). Also, the rest of the efficacy endpoints were comparable between subgroups: early change in NIHSS at day 1 (*p*=0.38) and odds of successful recanalization (*p*=0.75).

Regarding safety endpoints, we found some evidence that infarct growth velocity pattern influenced the effect of IVT+MT vs MT alone on the risk of any ICH on day 1 imaging (p-value for interaction < 0.001). Among slow progressors, treatment including prior IVT combined with MT was associated with lower odds of any ICH compared to MT alone (22.8 vs 36.4%; OR=0.52, 95% CI 0.27 - 0.98). Conversely, in the fast progressors subpopulation, the IVT+MT approach was associated with increased odds of any ICH (49.4 vs 26.8%; OR=2.62, 95% CI 1.42 - 4.82). We did not find evidence for effect heterogeneity with respect to symptomatic and asymptomatic ICH or mortality (*p*-values for interaction of 0.30, 0.32 and 0.32).

In the secondary analysis dividing population into quartiles of infarct growth velocity (**supplemental tables 1** & **2 and supplemental figures 1** & **2**), similar results were found. Indeed, no evidence for heterogeneity according to randomization arm was found regarding the odds of 3-month favorable outcome (*p*-value for interaction=0.63), change in NIHSS at day 1 (*p*-value for interaction=0.58), successful recanalization at the end of the endovascular procedure (*p*-value for interaction=0.96) and mortality (*p*=0.58). Whereas evidence for heterogeneity was found for the risk of any ICH (*p*-value for interaction = 0.001), decreased odds of any ICH were found in slow progressors treated with IVT+MT with respective OR (95% CI) in the two slower quartiles of 0.98 (0.40 - 2.39) and 0.26 (0.10 – 0.68). Conversely, as observed in the primary analysis, fast progressors treated with IVT+MT demonstrated an increased risk of any ICH occurrence with respective OR (95% CI) in two faster quartiles of 2.82 (1.21 – 6.59) and 2.14 (0.88 – 5.22) respectively. No significant interactions were detected between allocation to either IVT+MT or MT alone and the stroke progression pattern on the risk of symptomatic or asymptomatic ICH (respective *p*-values of interaction of 0.78 and 0.33).

The sensitivity analyses using “corrected ASPECTS” are presented in **supplemental figures 3** and **4**. Similar findings were observed in comparison to the primary and secondary analyses.

Main effect of infarct growth velocity:

Fast stroke progressors presented lower odds of favorable outcome after 90 days (69 vs 51%; OR=0.38; 95% CI 0.23 – 0.62; *p*<0.001) (**supplemental figure 5 and 6**). Also, NIHSS improved less in fast progressors (-8 vs -10; OR= 2.82; 95% CI 1.02 – 4.62; *p*=0.002). sICH risk was increased among fast progressors (5% vs 1%; OR=7.86, 95% CI 1.36 – 45.39; p=0.021). No evidence for differences were noted regarding the risk of any ICH (29 vs 38%; OR=1.26, 95% CI 0.79 – 2.02; *p*=0.33) and asymptomatic ICH (8 vs 7%; OR=1.09, 95% CI 0.48 – 2.49; *p*=0.84). Final successful recanalization rate tended to be lower (91 vs 95%; OR=0.42, 95% CI 0.17 – 1.03; *p*=0.06) and mortality rate tended to be higher (12 vs 6%; OR=2.16, 95% CI 0.98 – 4.79; *p*=0.06) among fast progressors. The "corrected ASPECTS" sensitivity analysis showed comparable results (see **supplemental figures 7** and **8**).

DISCUSSION:

In this post-hoc analysis of the SWIFT-DIRECT trial, we found no evidence of an interaction between the stroke progression velocity and the type of acute reperfusion strategy on the clinical outcome after 3 months. However, the infarct progression velocity significantly influenced the ICH occurrence: IVT+MT was associated with a lower ICH risk in slow progressors while increasing this risk among fast progressors. Also, we found additional evidence that fast stroke progression pattern was associated with worse clinical outcome and a higher risk of sICH irrespective to the treatment arm.

Previous studies already reported that stroke progression pattern was an important prognostic factor. Fast progressors are indeed usually associated with worse functional outcome[3–5,8,10]. In our analysis focused on the effect of infarct growth velocity on the entire SWIFT-DIRECT trial population, we also found that patients with a fast progression pattern presented significantly worse clinical outcomes than slow progressors. Interestingly, we also observed that stroke progression velocity was associated with ICH risk. To our knowledge, this was a novel finding that has not been reported to date. In the main effect analysis, fast progressors presented an

increased risk of sICH. Among available literature, the closest available information about this potential interaction was found in the publication by *Sarraj et al*[8]. In their study, odds of sICH among fast progressors were 10.6% while 4.5% in slow progressors, almost reaching statistical significance. The limited statistical power of their analysis might have influenced the non-significance (study population in this publication: n=285 including 85 patients in the fast progressors subgroup). In previous publications, extended time from stroke onset to reperfusion and lower initial ASPECTS has been separately reported associated with PH occurrence[16,17]. Studying stroke progression velocity actually allows regrouping these two characteristics into a unique indicator that might be a more sensitive and individualized feature for ICH risk prediction. This hypothesis deserves further focused studies.

In our opinion, the main result of this ancillary study was the interaction between the ischemic progression velocity and the type of acute reperfusion therapy (IVT+MT versus MT alone) on the odds of any ICH. Indeed, regarding this safety outcome, bridging strategy with IVT + MT was associated with a significantly lower risk of any ICH at day 1 in slow progressors. On the opposite, in the fast progressor subpopulation, IVT+MT strategy significantly increased the rate of any ICH. This might be a substantial warning. In addition to the increased sICH risk among fast progressors in the entire trial population, detecting an increased occurrence of ICH in the setting of prior IVT in fast progressors also treated with MT is a novel important finding. Indeed, it has been more and more established that ICH, even low grade and asymptomatic, is associated with worse functional outcomes[18–21]. Consequently, identifying factors predicting ICH occurrence is a meaningful challenge. There might be here an important signal toward a cautious use of IVT in fast progressors intended for MT[13,14]. Furthermore, in our study, the absence of statistically meaningful effect on sICH and aICH might likely be related to the lack of statistical power due to the relative rarity of such events in our study sample. Still, in comparison with any ICH, the directions of the statistical effect for sICH and aICH were similar but the occurrence of such ICH subtypes was too rare to reach significance and draw conclusions. Still, we think that our study does not provide sufficient evidence to withhold IVT

in fast progressors. Further randomized controlled trials should be considered to validate such findings. However, our results should encourage a close monitoring and management of others factors involved in ICH risk (arterial blood pressure, blood glucose level, antithrombotic medication, etc.) in fast progressors. There might also be an interest in the development neuroprotective drugs aiming to reduce ICH risk. Our finding may help to identify patients particularly eligible for such future therapies.

Multiple predictors of ICH, either symptomatic or asymptomatic, after thrombectomy have already been identified. In the literature, higher admission NIHSS, lower baseline ASPECTS and longer delay were reported associated with higher odds of ICH[10]. These factors are intrinsically associated with the fast progressor pattern, as our results also highlighted. The infarct growth velocity might actually constitute a tailored feature merging together distinct variables (baseline infarct core and delay) and potentially allowing to identify more precisely the individual ICH risk. Again, this hypothesis probably requires further exploration through dedicated studies but may be a promising perspective.

Our study presented several limitations. First, this was a post-hoc analysis and as such suffered from usual limitations in this setting. Then, only patients with baseline NIHSS ≥ 5, ASPECTS >5 and admitted before 4.5 hours after stroke onset were included in the SWIFT-DIRECT trial. Consequently, in this ancillary study, the definition of slow and fast progressors considered only patients treated in the early time window and presenting with relatively limited infarct core. Very fast progressors presenting with initial ASPECTS ≤5 within the first 4.5 hours after stroke onset were not included in the initial trial and consequently have not investigated in this sub analysis. Therefore, our results might not be extrapolated to patients presenting with initial ASPECTS of under 5 within the first 4.5 hours after symptom onset. This might be a selection bias. Extrapolation of our results to later time window or more extended infarct core should be considered with caution. Also, our definition of stroke progression velocity was based on ASPECTS. ASPECTS were collected using either DWI or CT. This may have introduce some bias regarding sensitivity of each modality in quantifying initial ASPECTS. However,

these two imaging modalities were perfectly balanced in the global study population and among subgroups. Perfusion imaging and absolute core volumes were not available to determine initial stroke extension and calculate more precisely the infarct progression speed. Still, performance in infarct core estimation of diffusion weighted imaging or non-contrast CT has been reported to be very close from perfusion imaging[22]. Collateral circulation status is an intrinsic component of infract growth velocity, with a collinear effect[9]. However, these data were not collected in the SWIFT-DIRECT trial and the influence of this variable was not analyzed in our study. Finally, due to the sample size, some analysis may have lack of power, especially considering rare events such as sICH.

CONCLUSION:

In this subanalysis of the SWIFT-DIRECT trial, we did not find evidence for a significant interaction of the velocity of infarct growth and the type of acute reperfusion therapy (MT alone or combined IVT + MT) on the odds of favourable outcome. However, prior IVT combined with MT was associated with significantly reduced the occurrence of any ICH among slow progressors whereas increased in fast progressors. Further studies should investigate the influence of stroke progression pattern and the type of acute reperfusion therapy on the risk of ICH.

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Table 1: Baseline characteristics by stroke progression groups (based on the median of ASPECTS decay)

	Total	Total	<1.2 pt/h	<1.2 pt/h	>1.2 pt/h	>1.2 pt/h	P-value
	N*	(N = 376)	N*	(N = 189)	N*	(N = 187)	
Group - no. (%)	376		189		187		0.35
Thrombectomy alone		185 (49.2%)		88 (46.6%)		97 (51.9%)	
Alteplase plus thrombectomy		191 (50.8%)		101 (53.4%)		90 (48.1%)	
Treatment received - no. (%)	376		189		187		0.41
Thrombectomy alone		184 (48.9%)		88 (46.6%)		96 (51.3%)	
Alteplase plus thrombectomy		192 (51.1%)		101 (53.4%)		91 (48.7%)	
Age at inclusion - median (IQR)	376	73 (65, 81)	189	75 (67, 82)	187	71 (62, 78)	0.004
Female sex - no. (%)	376	195 (51.9%)	189	107 (56.6%)	187	88 (47.1%)	0.08
Admission NIHSS - median (IQR)	376	17 (13, 20)	189	16 (12, 19)	187	18 (14, 21)	<0.001
Pre-stroke mRS - no. (%)	376		189		187		1.00
0		319 (84.8%)		160 (84.7%)		159 (85.0%)	
1		56 (14.9%)		28 (14.8%)		28 (15.0%)	
4		1 (0.3%)		1 (0.5%)		0 (0.0%)	
Weight (kg) - median (IQR)	353	75 (65, 85)	185	74 (64, 83)	168	75 (66, 85)	0.13
Systolic blood pressure (mmHg) - median (IQR)	372	148 (132, 163)	187	150 (134, 168)	185	147 (130, 160)	0.16
Diastolic blood pressure (mmHg) - median (IQR)	369	80 (70, 90)	185	80 (71, 90)	184	80 (70, 91)	0.68
Heart rate (beats per minute) - median (IQR)	366	74 (63, 88)	182	76 (64, 88)	184	74 (63, 87)	0.44
Risk factors							
Previous ischemic stroke - no. (%)	362	38 (10.5%)	183	19 (10.4%)	179	19 (10.6%)	1.00
Previous transient ischemic attack - no. (%)	357	21 (5.9%)	182	15 (8.2%)	175	6 (3.4%)	0.07
History of hypertension - no. (%)	366	229 (62.6%)	184	106 (57.6%)	182	123 (67.6%)	0.05
History of atrial fibrillation - no. (%)	355	36 (10.1%)	178	17 (9.6%)	177	19 (10.7%)	0.73
History of hypercholesterolemia - no. (%)	355	123 (34.6%)	176	58 (33.0%)	179	65 (36.3%)	0.58
Previous intracerebral hemorrhage - no. (%)	365	2 (0.5%)	188	1 (0.5%)	177	1 (0.6%)	1.00
Prior myocardial infarction - no. (%)	359	40 (11.1%)	182	16 (8.8%)	177	24 (13.6%)	0.18
Medication							
Warfarin or other anticoagulant - no. (%)	376	13 (3.5%)	189	5 (2.6%)	187	8 (4.3%)	0.41
Aspirin - no. (%)	376	98 (26.1%)	189	48 (25.4%)	187	50 (26.7%)	0.81
Statine or other lipid lowering agent - no. (%)	376	112 (29.8%)	189	54 (28.6%)	187	58 (31.0%)	0.65

Lab values							
Blood glucose level (mmol/L) - median (IQR)	355	6.6 (5.8, 7.6)	174	6.5 (5.7, 7.5)	181	6.7 (5.8, 7.7)	0.34
International normalized ratio (INR) - median (IQR)	294	1.0 (1.0, 1.1)	146	1.0 (1.0, 1.1)	148	1.0 (1.0, 1.1)	0.70
Platelet count x 10 E9(G/L) - median (IQR)	373	225 (187, 269)	187	222 (185, 268)	186	228 (188, 272)	0.37
Hemoglobin (g/L) - median (IQR)	376	137 (125, 146)	189	137 (125, 144)	187	137 (125, 149)	0.52
Glomerular filtration rate (mL/min) - median (IQR)	376	76 (62, 90)	189	74 (60, 88)	187	77 (62, 90)	0.26
Imaging							
Baseline imaging - no. (%)	376		189		187		0.97
CT		185 (49.2%)		93 (49.2%)		92 (49.2%)	
MRI		188 (50.0%)		95 (50.3%)		93 (49.7%)	
both		3 (0.8%)		1 (0.5%)		2 (1.1%)	
ASPECTS (core lab) - median (IQR)	376	8.0 (7.0, 9.0)	189	9.0 (8.0, 9.0)	187	7.0 (6.0, 8.0)	<0.001
Baseline intracranial occlusion site - no. (%)	376		189		187		0.37
Distal ICA - I		14 (3.7%)		8 (4.2%)		6 (3.2%)	
Distal ICA - I and M1		2 (0.5%)		2 (1.1%)		0 (0.0%)	
Distal ICA - L		52 (13.8%)		24 (12.7%)		28 (15.0%)	
Distal ICA - T		39 (10.4%)		14 (7.4%)		25 (13.4%)	
Distal M1		113 (30.1%)		64 (33.9%)		49 (26.2%)	
Distal M2		4 (1.1%)		2 (1.1%)		2 (1.1%)	
Proximal M1		135 (35.9%)		67 (35.4%)		68 (36.4%)	
Proximal M2		17 (4.5%)		8 (4.2%)		9 (4.8%)	
Distal occlusion sites - no. (%)	376		189		187		0.16
no		242 (64.4%)		115 (60.8%)		127 (67.9%)	
yes		134 (35.6%)		74 (39.2%)		60 (32.1%)	
Tandem lesion - no. (%)	376	57 (15.2%)	189	34 (18.0%)	187	23 (12.3%)	0.15
Timelines							
Time from stroke onset to randomisation (min) - median (IQR)	376	129 (100, 170)	189	142 (108, 184)	187	117 (92, 146)	<0.001
Time from arrival at emergency department to IV t-PA (min) - median (IQR)	192	54 (36, 72)	101	50 (32, 77)	91	55 (39, 70)	0.89
Door-to-puncture time (min) - median (IQR)	376	77 (61, 94)	189	77 (60, 99)	187	77 (61, 90)	0.53
Time from randomization to groin puncture (min) - median (IQR)	376	28 (20, 38)	189	28 (21, 38)	187	28 (19, 38)	0.70
Time from start of intravenous alteplase to groin puncture (min) - median (IQR)	192	24 (15, 35)	101	24 (15, 35)	91	24 (15, 35)	0.88

N*: number of patients with non-missing data

Table 2: Procedural characteristics in stroke progression subgroups

	Total	Total	<1.2 pt/h	<1.2 pt/h	>1.2 pt/h	>1.2 pt/h	P-value
	N*	(N = 376)	N*	(N = 189)	N*	(N = 187)	
Number of passes - median (IQR)	376	1.0 (1.0, 2.5)	189	1.0 (1.0, 2.0)	187	1.0 (1.0, 3.0)	0.49
Any mechanical device used - no. (%)	376	369 (98.1%)	189	186 (98.4%)	187	183 (97.9%)	0.72
Mechanical thrombectomy performed - no. (%)	376	356 (94.7%)	189	178 (94.2%)	187	178 (95.2%)	0.82
Balloon guide catheter used - no. (%)	375	165 (44.0%)	189	86 (45.5%)	186	79 (42.5%)	0.60
Distal aspiration catheter used - no. (%)	375	281 (74.9%)	189	140 (74.1%)	186	141 (75.8%)	0.72
Extracranial Stenting - no. (%)	375	35 (9.3%)	189	18 (9.5%)	186	17 (9.1%)	1.00
Peri-Interventional Aspirin - no. (%)	374	38 (10.2%)	189	18 (9.5%)	185	20 (10.8%)	0.73
Further thrombectomy device used after Solitaire - no. (%)	376	110 (29.3%)	189	52 (27.5%)	187	58 (31.0%)	0.50
Conscious sedation - no. (%)	376	183 (48.7%)	189	103 (54.5%)	187	80 (42.8%)	0.024
General anesthesia - no. (%)	376	169 (44.9%)	189	69 (36.5%)	187	100 (53.5%)	0.001
Reason for general anesthesia - no. (%)	169		69		100		0.72
Hospital standard practice		128 (75.7%)		51 (73.9%)		77 (77.0%)	
Clinically indicated		41 (24.3%)		18 (26.1%)		23 (23.0%)	

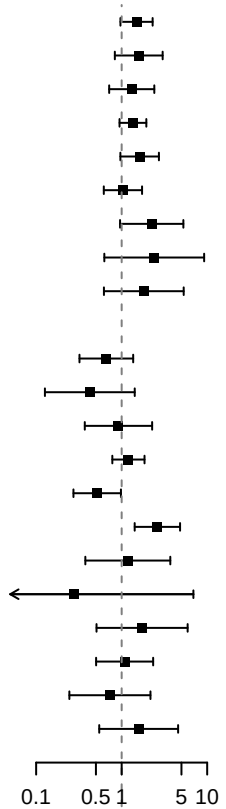
N*: number of patients with non-missing data

Figure legends:

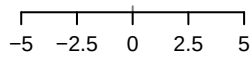
Figure 1: The effect of allocation to Alteplase plus thrombectomy vs Thrombectomy alone for each stroke progression group (based on the median of ASPECTS decay), as marginal odds ratio or mean difference with 95% confidence interval (CI). Calculated from Firth logistic and linear regression models adjusted for stratification factors and sex.

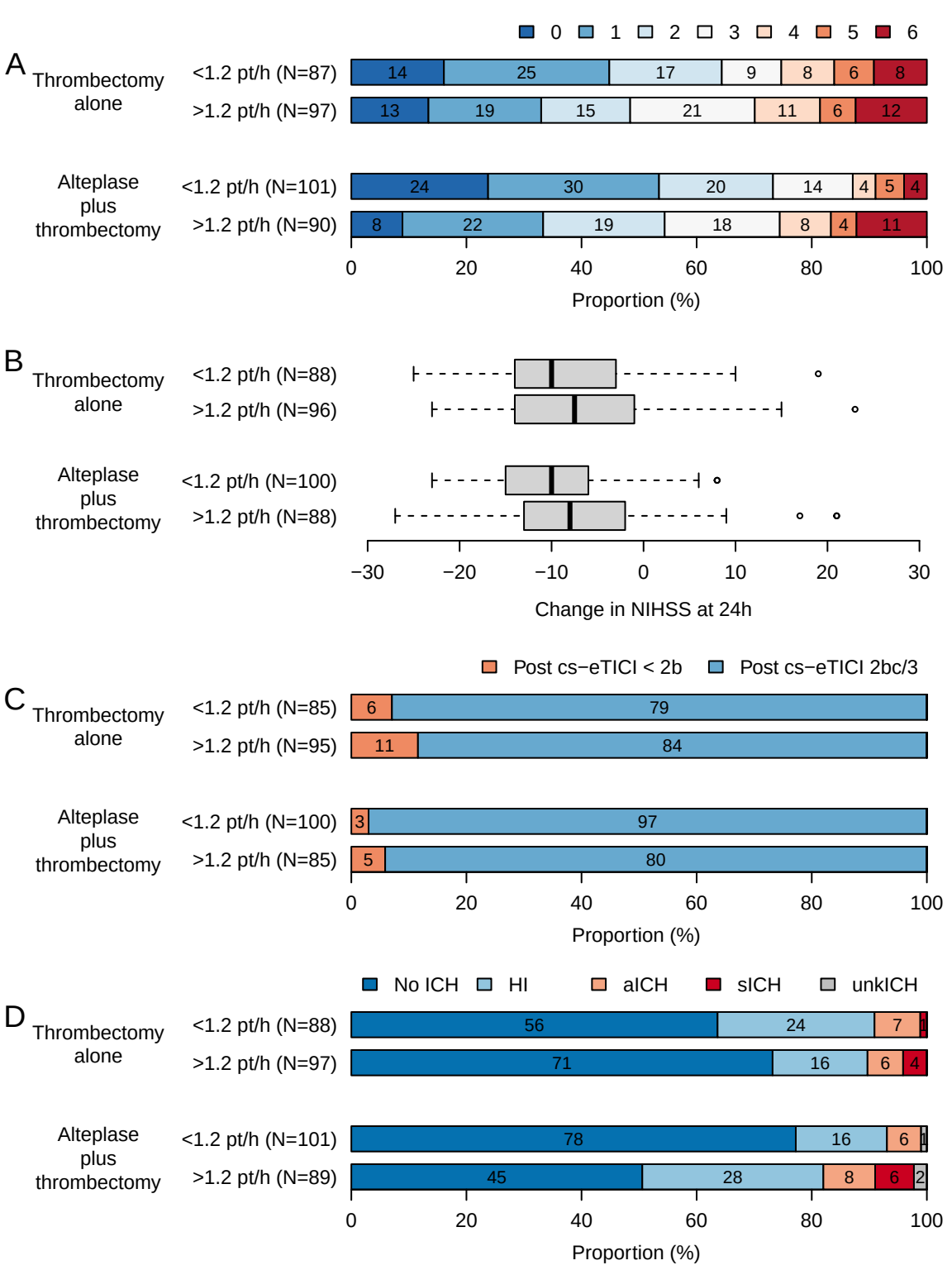
Figure 2: Descriptives for primary and secondary outcomes by stroke progression group (based on the median of ASPECTS decay) and intervention (IVT+MT vs MT alone). (A) Modified Rankin scale (mRS) at the 90 day visit, (B) change in NHSS at day 1, (C) successful recanalization (cs-eTICI 2b, 2c or 3), (D) intracranial hemorrhage (ICH) on day 1 imaging, separated in hemorrhagic infarction (HI), asymptomatic ICH (aICH), symptomatic ICH (sICH) and ICH with unknown symptomatic (unkICH).

	N	Thrombectomy alone n/N (%) or median [IQR]	Alteplase plus thrombectomy n/N (%) or median [IQR]	Odds ratio (95% CI)	P−value	P−value for interaction
mRS 0−2 at 90 days	375	103/184 (56.0%)	123/191 (64.4%)	1.49 (0.97 to 2.30)	0.07	
<1.2 pt/h	188	56/87 (64.4%)	74/101 (73.3%)	1.58 (0.83 to 3.01)	0.16	0.68
>1.2 pt/h	187	47/97 (48.5%)	49/90 (54.4%)	1.31 (0.71 to 2.41)	0.38	
mRS at 90 days	375	2.0 [1.0 to 4.0]	2.0 [1.0 to 3.0]	1.35 (0.94 to 1.94)	0.10	
<1.2 pt/h	188	2.0 [1.0 to 4.0]	1.0 [1.0 to 3.0]	1.62 (0.97 to 2.73)	0.07	0.22
>1.2 pt/h	187	3.0 [1.0 to 4.0]	2.0 [1.0 to 4.0]	1.03 (0.62 to 1.73)	0.90	
Final cs−eTICI 2bc/3	365	163/180 (90.6%)	177/185 (95.7%)	2.25 (0.96 to 5.27)	0.06	
<1.2 pt/h	185	79/85 (92.9%)	97/100 (97.0%)	2.40 (0.63 to 9.21)	0.20	0.75
>1.2 pt/h	180	84/95 (88.4%)	80/85 (94.1%)	1.82 (0.62 to 5.31)	0.28	
Mortality at 90 days	375	20/184 (10.9%)	15/191 (7.9%)	0.66 (0.32 to 1.36)	0.26	
<1.2 pt/h	188	8/87 (9.2%)	4/101 (4.0%)	0.42 (0.13 to 1.42)	0.16	0.32
>1.2 pt/h	187	12/97 (12.4%)	11/90 (12.2%)	0.92 (0.37 to 2.27)	0.85	
Any ICH at 24h	375	58/185 (31.4%)	67/190 (35.3%)	1.20 (0.78 to 1.85)	0.41	
<1.2 pt/h	189	32/88 (36.4%)	23/101 (22.8%)	0.52 (0.27 to 0.98)	0.043	<0.001
>1.2 pt/h	186	26/97 (26.8%)	44/89 (49.4%)	2.62 (1.42 to 4.82)	0.002	
Symptomatic ICH at 24h	372	5/185 (2.7%)	6/187 (3.2%)	1.18 (0.38 to 3.70)	0.78	
<1.2 pt/h	188	1/88 (1.1%)	0/100 (0.0%)	0.28 (0.01 to 6.90)	0.44	0.30
>1.2 pt/h	184	4/97 (4.1%)	6/87 (6.9%)	1.73 (0.51 to 5.91)	0.38	
Asymptomatic ICH at 24h	372	13/185 (7.0%)	14/187 (7.5%)	1.08 (0.50 to 2.33)	0.84	
<1.2 pt/h	188	7/88 (8.0%)	6/100 (6.0%)	0.73 (0.24 to 2.17)	0.57	0.32
>1.2 pt/h	184	6/97 (6.2%)	8/87 (9.2%)	1.58 (0.55 to 4.57)	0.40	



	N	Thrombectomy alone median [IQR]	Alteplase plus thrombectomy median [IQR]	Mean difference (95% CI)	P−value	P−value for interaction
Change in NIHSS at 24h	372	−9.0 [−14.0 to −2.0]	−9.0 [−15.0 to −4.0]	−0.72 (−2.31 to 0.87)	0.37	
<1.2 pt/h	188	−10.0 [−14.0 to −3.0]	−10.0 [−15.0 to −6.0]	−1.22 (−3.08 to 0.65)	0.20	0.38
>1.2 pt/h	184	−7.5 [−14.0 to −1.0]	−8.0 [−13.0 to −2.0]	0.20 (−2.34 to 2.74)	0.88	




A
Thrombectomy alone
<1.2 pt/h (N=87)
>1.2 pt/h (N=97)
Alteplase plus thrombectomy
<1.2 pt/h (N=101)
>1.2 pt/h (N=90)
0 1 2 3 4 5 6
14 25 17 9 8 6 8
13 19 15 21 11 6 12
24 30 20 14 4 5 4
8 22 19 18 8 4 11
0 20 40 60 80 100
Proportion (%)
B
Thrombectomy alone
<1.2 pt/h (N=88)
>1.2 pt/h (N=96)
Alteplase plus thrombectomy
<1.2 pt/h (N=100)
>1.2 pt/h (N=88)
−30 −20 −10 0 10 20 30
Change in NIHSS at 24h
C
Post cs−eTICI < 2b
Post cs−eTICI 2bc/3
Thrombectomy alone
<1.2 pt/h (N=85)
>1.2 pt/h (N=95)
Alteplase plus thrombectomy
<1.2 pt/h (N=100)
>1.2 pt/h (N=85)
6 79
11 84
3 97
5 80
0 20 40 60 80 100
Proportion (%)
D
No ICH
HI
aICH
sICH
unkICH
Thrombectomy alone
<1.2 pt/h (N=88)
>1.2 pt/h (N=97)
Alteplase plus thrombectomy
<1.2 pt/h (N=101)
>1.2 pt/h (N=89)
56 24 7 1
71 16 6 4
78 16 6 1
45 28 8 6 2
0 20 40 60 80 100
Proportion (%)