



HAL
open science

Time to treatment with bridging intravenous alteplase before endovascular treatment:subanalysis of the randomized controlled SWIFT-DIRECT trial

T. R. Meinel, J. Kaesmacher, L. Buetikofer, D. Strbian, O. F. Eker, C. Cognard, P. Mordasini, S. Deppeler, V. Mendes Pereira, J. F. Albucher, et al.

► To cite this version:

T. R. Meinel, J. Kaesmacher, L. Buetikofer, D. Strbian, O. F. Eker, et al.. Time to treatment with bridging intravenous alteplase before endovascular treatment:subanalysis of the randomized controlled SWIFT-DIRECT trial. *Journal of Neurointerventional Surgery*, 2023, 15 (e1), pp.e102-e110. 10.1136/jnis-2022-019207 . inserm-03831078

HAL Id: inserm-03831078

<https://inserm.hal.science/inserm-03831078>

Submitted on 26 Oct 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Original research

Time to treatment with bridging intravenous alteplase before endovascular treatment: subanalysis of the randomized controlled SWIFT-DIRECT trial

Thomas R Meinel ,¹ Johannes Kaesmacher ,² Lukas Buetikofer,³ Daniel Strbian,⁴ Omer Faruk Eker,⁵ Christophe Cognard ,⁶ Pasquale Mordasini,² Sandro Deppeler,⁷ Vitor Mendes Pereira ,⁸ Jean François Albucher,⁹ Jean Darcourt ,⁵ Romain Bourcier,¹⁰ Benoit Guillon,¹¹ Chrysanthi Papagiannaki ,¹² Guillaume Costentin,¹³ Gerli Sibolt,⁴ Silja Rätty,⁴ Benjamin Gory,¹⁴ Sébastien Richard ,¹⁵ Jan Liman,¹⁶ Marielle Ernst,¹⁷ Marion Boulanger,¹⁸ Charlotte Barbier,¹⁹ Laura Mechtouff ,²⁰ Liqun Zhang,²¹ Gaultier Marnat ,²² Igor Sibon,²³ Omid Nikoubashman ,²⁴ Arno Reich,²⁵ Arturo Consoli,²⁶ David Weisenburger,²⁶ Manuel Requena ,^{27,28} Alvaro Garcia-Tornel ,²⁷ Suzana Saleme,²⁹ Solène Moulin,³⁰ Paolo Pagano ,³¹ Guillaume Saliou ,³² Emmanuel Carrera,³³ Kevin Janot ,³⁴ Marti Boix,³⁵ Raoul Pop ,³⁶ Lucie Della Schiava,³⁷ Andreas Luft,^{38,39} Michel Piotin,⁴⁰ Jean Christophe Gentric,⁴¹ Aleksandra Pikula,⁴² Waltraud Pfeilschifter,⁴³ Marcel Arnold,¹ Adnan Siddiqui,⁴⁴ Michael T Froehler,⁴⁵ Anthony J Furlan,⁴⁶ René Chapot,⁴⁷ Martin Wiesmann ,²⁴ Paolo Machi,⁴⁸ Hans-Christoph Diener,⁴⁹ Zsolt Kulcsar,⁵⁰ Leo Bonati,⁵¹ Claudio Bassetti,¹ Simon Escalard,⁴⁰ David Liebeskind ,⁵² Jeffrey L Saver ,⁵² Urs Fischer,^{1,51} Jan Gralla,² on behalf of the SWIFT-DIRECT investigators

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/jnis-2022-019207>).

For numbered affiliations see end of article.

Correspondence to

Dr Urs Fischer, Department of Neurology, Inselspital Universitätsspital Bern, Bern, Switzerland; urs.fischer@usb.ch

TRM and JK contributed equally.

Received 1 June 2022
Accepted 13 July 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Meinel TR, Kaesmacher J, Buetikofer L, et al. *J NeuroIntervent Surg* Epub ahead of print: [please include Day Month Year]. doi:10.1136/neurintsurg-2022-019207

ABSTRACT

Background We hypothesized that treatment delays might be an effect modifier regarding risks and benefits of intravenous thrombolysis (IVT) before mechanical thrombectomy (MT).

Methods We used the dataset of the SWIFT-DIRECT trial, which randomized 408 patients to IVT+MT or MT alone. Potential interactions between assignment to IVT+MT and expected time from onset-to-needle (OTN) as well as expected time from door-to-needle (DTN) were included in regression models. The primary outcome was functional independence (modified Rankin Scale (mRS) 0–2) at 3 months. Secondary outcomes included mRS shift, mortality, recanalization rates, and (symptomatic) intracranial hemorrhage at 24 hours.

Results We included 408 patients (IVT+MT 207, MT 201, median age 72 years (IQR 64–81), 209 (51.2%) female). The expected median OTN and DTN were 142 min and 54 min in the IVT+MT group and 129 min and 51 min in the MT alone group. Overall, there was no significant interaction between OTN and bridging IVT assignment regarding either the functional (adjusted OR (aOR) 0.76, 95% CI 0.45 to 1.30) and safety outcomes or the recanalization rates. Analysis of in-hospital delays showed no significant interaction between DTN and bridging IVT assignment regarding the dichotomized functional outcome (aOR 0.48, 95% CI 0.14 to 1.62),

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Overall, the randomized controlled trials on bridging thrombolysis before mechanical thrombectomy did not report any clear subgroup effects related to the time from symptom onset to randomization.

WHAT THIS STUDY ADDS

⇒ This study found no clear evidence that patients with short onset-to-needle times benefited more from bridging thrombolysis. Exploratory analysis of secondary clinical outcomes indicated a potentially favorable effect of IVT associated with shorter in-hospital delays.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study sets methodological benchmarks for analyzing the heterogeneity of bridging thrombolysis effect size before mechanical thrombectomy in a meta-analysis of all randomized controlled trials on this topic. Neither onset-to-needle times nor door-to-needle times should influence treatment decisions regarding bridging thrombolysis until this meta-analysis is available.

but the shift and mortality analyses suggested a greater benefit of IVT when in-hospital delays were short.

Conclusions We found no evidence that the effect of bridging IVT on functional independence is modified by overall or in-hospital treatment delays. Considering its low power, this subgroup analysis could have missed a clinically important effect, and exploratory analysis of secondary clinical outcomes indicated a potentially favorable effect of IVT with shorter in-hospital delays. Heterogeneity of the IVT effect size before MT should be further analyzed in individual patient meta-analysis of comparable trials.

Trial registration number URL: <https://www.clinicaltrials.gov> ; Unique identifier: NCT03192332

INTRODUCTION

Whether mechanical thrombectomy (MT) alone can be regarded as equally effective as MT combined with bridging intravenous thrombolysis (IVT+MT) for patients admitted directly to centers with endovascular treatment capability remains controversial.^{1,2} Two trials in Chinese patients demonstrated non-inferiority of MT alone,^{3,4} whereas three other trials failed to show non-inferiority.⁵⁻⁷ All these trials used generous non-inferiority margins, which are considerably less conservative than the proposed minimal clinically important difference or the margin considered to constitute reasonable comparability⁸. The expedited recommendation of the European Stroke Organisation currently advises that patients admitted to MT-capable centers should undergo IVT+MT if eligible for both treatments.⁹

None of the individual subgroup analyses of these trials showed a significant difference regarding time from onset of symptoms to randomization (OTR). However, the point estimates indicated a potential time-dependent relationship between bridging IVT and functional outcome (table 1). In unselected stroke patients, the efficacy of IVT is known to be highly time-dependent.¹⁰ Therefore, we hypothesized that treatment delays might be an effect modifier regarding risks and benefits of IVT in patients enrolled in the SWIFT-DIRECT trial⁷ and that a more beneficial effect of IVT would be seen in patients with shorter treatment delays.

This analysis aimed to assess a potential treatment effect heterogeneity of IVT+MT versus MT alone according to the overall delay (onset-to-needle, OTN) and in-hospital delays (door-to-needle, DTN) in terms of functional outcome, technical efficacy and safety outcomes. Additionally, if a heterogeneity of treatment effect was found, we intended to characterize the extent to which modification occurs and the time period during which adding IVT might confer significant benefits.

METHODS

Reporting, data sharing, ethics

For this post-hoc sub-analysis of the randomized controlled SWIFT-DIRECT study (<https://clinicaltrials.gov/NCT03192332>), we followed the CONSORT (Consolidated Standards of Reporting Trials) guidelines. The SWIFT-DIRECT dataset is not publicly available. However, de-identified data, together with a data dictionary, will be made accessible after ethics clearance and on submission of a reasonable request with a research plan to the corresponding author. Written informed consent was obtained from patients or their next of kin, with selected countries allowing delayed informed consent due to emergency circumstances. Approval was obtained from all relevant local ethics committees (central ethics Bern, ID 2017-00974).

Study design and patients

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 protocol¹¹ and main results, including details of the methodology, have already been published.⁷ Patients were eligible if they had imaging-confirmed occlusion of the intracranial carotid artery and/or the first segment (M1) of the middle cerebral artery; were eligible to receive alteplase within 4.5 hours after they were last seen well; could undergo MT within 75 min of randomization; and had severe neurological deficits, defined as a National Institutes of Health Stroke Scale (NIHSS) score of ≥ 5 . Patients with advanced dementia, significant pre-existing disabilities, and early severe tissue damage (Alberta Stroke Programme Early CT Score (ASPECTS) < 5) were excluded. 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). We included all patients in this post-hoc analysis.

Time definitions

The goal of our study was to assess whether time to treatment was an effect modifier—that is, it would have an impact on the effect of IVT plus MT versus MT alone—with the idea that, depending on the time to treatment, additional IVT might show a benefit compared with MT alone. The time interval analyzed for the overall time delay was hence the expected OTN. This was defined as time from symptom onset or last known well to expected IVT bolus. It was calculated by adding the mean randomization-to-bolus-time to the onset-to-randomization

Table 1 Subgroup analysis of published randomized controlled trials

Study	Source	Outcome	Subgroup	aOR/aOR point estimate (95% CI)
MRCLEAN-NoIV ⁵	online supplemental figure S3	Ordinal mRS score	OTR 13–77 min OTR 77–124 min OTR 124–734	0.75 (0.43 to 1.31) 0.67 (0.39 to 1.15) 1.00 (0.58 to 1.73)
DIRECT-MT ¹⁸	online supplemental figure S4	Ordinal mRS score	OTR ≤ 125 min OTR 126–171 min OTR 172–210 min OTR > 210 min	0.93 (0.54 to 1.61) 0.94 (0.54 to 1.64) 1.28 (0.74 to 2.22) 1.38 (0.79 to 2.40)
DEVT ¹⁹	online supplemental eFigure 6	mRS 0–2	OTR < 169 min OTR ≥ 169 min	0.97 (0.41 to 2.3) 2.25 (0.88 to 6.05)
SKIP ⁶	Main paper figure 3	mRS 0–2	OTR < 120 min OTR ≥ 120 min	0.77 (0.33 to 1.78) 1.33 (0.61 to 2.87)

In all trials a higher aOR/acOR favors withholding bridging IVT, while a lower aOR/acOR favors administering IVT before MT. acOR, adjusted common OR; aOR, adjusted OR; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; OTR, onset-to-randomization time.

Table 2 Selected baseline characteristics according to time from symptom onset to needle

	Time from symptom onset to needle				P value
	0–3 hours (n=316)		>3 hours (n=92)		
	N*		N*		
Age at inclusion (years), median (IQR)	316	72 (64–81)	92	74 (67–81)	0.27
Female sex, no. (%)	316	159 (50.3%)	92	50 (54.3%)	0.55
NIHSS, median (IQR)	316	17 (13–20)	92	17 (12–20)	0.8
Pre-stroke mRS, no. (%)	316		92		0.8
		269 (85.1%)		77 (83.7%)	
		46 (14.6%)		15 (16.3%)	
		1 (0.3%)		0 (0.0%)	
Weight (kg), median (IQR)	293	75 (65–85)	89	75 (68–85)	0.81
Systolic blood pressure (mmHg), median (IQR)	312	147 (130–160)	91	149 (135–163)	0.58
Diastolic blood pressure (mmHg), median (IQR)	310	80 (70–90)	90	80 (71–90)	0.99
Heart rate (beats/min), median (IQR)	309	75 (64–88)	88	74 (63–86)	0.86
Previous ischemic stroke, no. (%)	304	30 (9.5%)	90	11 (12.0%)	0.55
Previous transient ischemic attack, no. (%)	300	14 (4.4%)	89	7 (7.6%)	0.28
History of hypertension, no. (%)	306	185 (58.5%)	92	54 (58.7%)	1
History of atrial fibrillation, no. (%)	299	28 (8.9%)	88	11 (12.0%)	0.42
History of hypercholesterolemia, no. (%)	298	98 (31.0%)	89	33 (35.9%)	0.38
Previous intracerebral hemorrhage, no. (%)	307	2 (0.6%)	90	0 (0.0%)	1
Prior myocardial infarction, no. (%)	301	37 (11.7%)	89	4 (4.3%)	0.047
Warfarin or other anticoagulant, no. (%)	316	11 (3.5%)	92	5 (5.4%)	0.37
Aspirin, no. (%)	316	84 (26.6%)	92	21 (22.8%)	0.5
Statin or other lipid lowering agent, no. (%)	316	91 (28.8%)	92	28 (30.4%)	0.79
Blood glucose level (mmol/L), median (IQR)	303	6.5 (5.7–7.5)	82	6.6 (5.9–7.6)	0.46
INR, median (IQR)	253	1.0 (1.0–1.1)	67	1.0 (1.0–1.1)	0.62
Platelet count ($\times 10^9/L$), median (IQR)	314	225 (187–268)	91	228 (192–280)	0.28
Hemoglobin (g/L), median (IQR)	316	137 (125–146)	92	137 (123–147)	0.84
Glomerular filtration rate (mL/min), median (IQR)	316	76 (62–90)	92	74 (60–90)	0.89
Baseline imaging, no. (%)	316		92		<0.001
CT		177 (56.0%)		28 (30.4%)	
MRI		137 (43.4%)		63 (68.5%)	
Both		2 (0.6%)		1 (1.1%)	
ASPECTS (core lab), median (IQR)	315	8.0 (7.0–9.0)	92	8.0 (6.0–8.5)	0.004
Baseline intracranial occlusion site, no. (%)	316		92		0.99

Continued

Table 2 Continued

	Time from symptom onset to needle				P value
	0–3 hours (n=316)		>3 hours (n=92)		
	N*		N*		
Distal ICA - I	12 (3.8%)		4 (4.3%)		
Distal ICA - I and M1	2 (0.6%)		0 (0.0%)		
Distal ICA - L	41 (13.0%)		13 (14.1%)		
Distal ICA - T	37 (11.7%)		8 (8.7%)		
Distal M1	96 (30.4%)		29 (31.5%)		
Distal M2	3 (0.9%)		1 (1.1%)		
Proximal M1	110 (34.8%)		34 (37.0%)		
Proximal M2	15 (4.7%)		3 (3.3%)		
Tandem lesion, no. (%)	316	45 (14.2%)	92	18 (19.6%)	0.25

ASPECTS, Alberta Stroke Programme Early CT Score; ICA, internal carotid artery; INR, International normalized ratio; mRS, modified Rankin Scale; N*, number of patients with non-missing data; NIHSS, National Institutes of Health Stroke Scale.

value, for each patient in both the MT alone and the IVT+MT treatment groups.

For the in-hospital delay, the expected DTN was analyzed. This was defined as the time from arrival at the emergency department of the study hospital to the expected IVT bolus. It was calculated by adding to the door-to-randomization value, for each patient in both the MT alone and IVT+MT groups, the study mean for the randomization to bolus time. Those

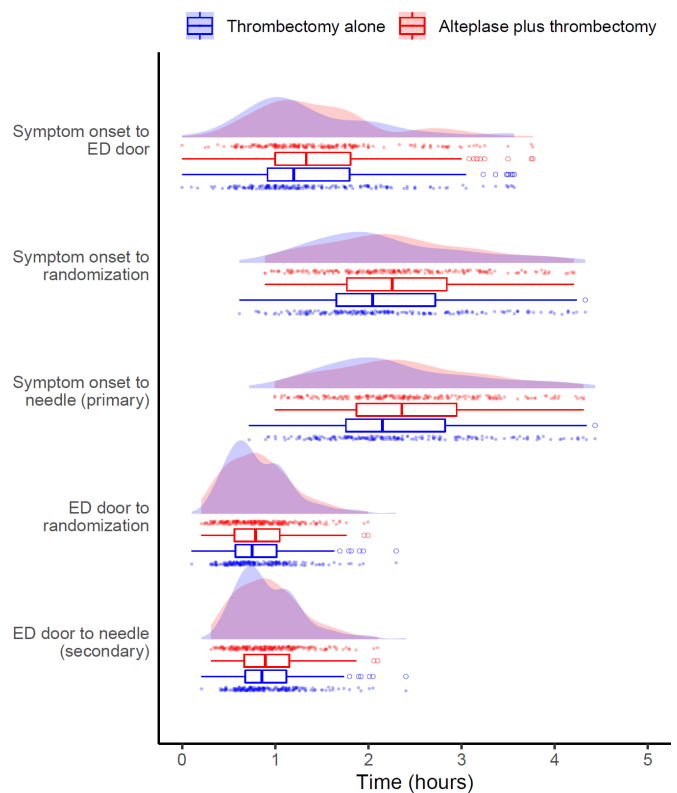


Figure 1 Distribution of time to treatment variables by randomization group. The median expected onset-to-needle time was 135 min (IQR 107–176) and the median expected door-to-needle time 53 min (IQR 40–69), without significant differences between both arms. The expected times were calculated as specified in the methods. For one patient the randomization date was interpolated. ED, emergency department.

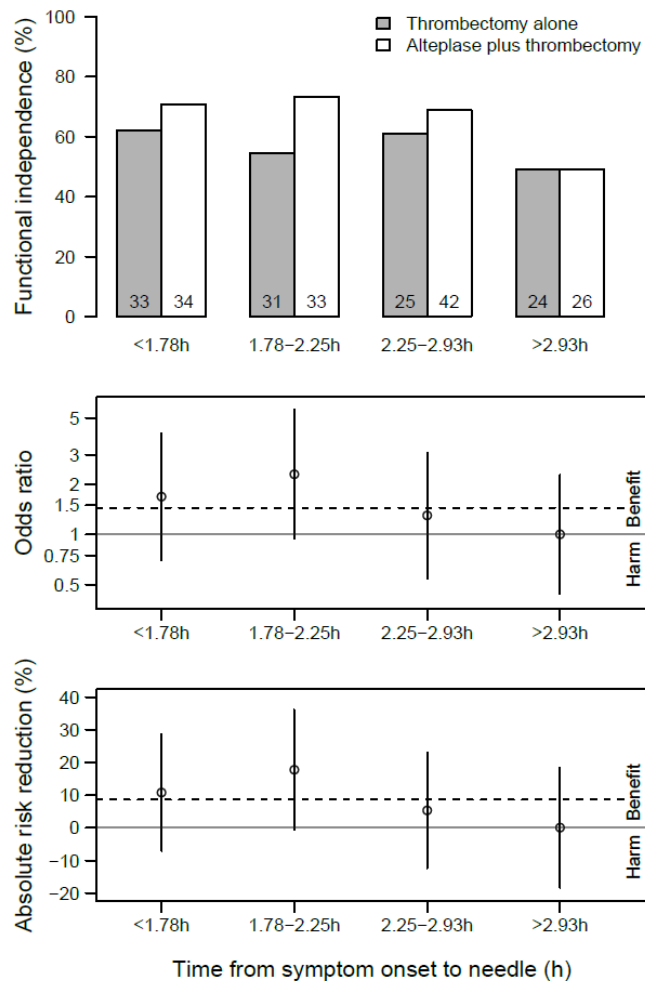


Figure 2 Benefit according to quartiles of expected time from symptom onset to last known well to IVT bolus. (Top panel) Event rates of functional independence (%), (N). (Middle panel) Odds ratios of IVT+MT versus MT alone with the dashed line indicating the marginal effect over all categories and the gray line the zero effect. (Bottom panel) Absolute risk reduction for IVT+MT versus MT alone. Benefit and harm refer to combination of IVT+MT versus MT alone. IVT, intravenous thrombolysis; MT, mechanical thrombectomy.

somewhat artificial time intervals were chosen since they represent the clinical scenario outside randomized controlled trials better than onset-to-randomization and door-to-randomization times. They are therefore easier to interpret and applicable to stroke centers. The study mean of DTN time was used due to the small sample sizes at individual centers and because there was little variation across sites. As a post-hoc sensitivity analysis, we used the individual time to IVT bolus administration for patients who received this treatment.

Outcomes

Detailed definitions are available in the statistical analysis plan that was finalized and deposited¹² before the analysis. The primary endpoint was functional independence, defined as modified Rankin Scale (mRS) ≤2 at 90 days. Secondary outcomes included mRS shift analysis, all-cause mortality, and time-to-reperfusion defined as expanded Thrombolysis In Cerebral Infarction (eTICI ≥2b). We also analyzed pharmacological efficacy (pre-interventional cross-sectional eTICI ≥2a (cs-eTICI), technical efficacy (eTICI ≥2b following device use) and safety

outcomes (any and symptomatic intracranial hemorrhage, with the latter defined as ≥4 points worsening on the NIHSS within 24 hours).¹³

Statistical analysis

An independent statistician (LB) organized, cleaned and analyzed the data according to the prespecified statistical analysis plan (see the online supplemental material). The intention-to-treat population was analyzed for a potential time- and IVT-arm-assignment interaction by comparing the outcomes in the IVT arm to the outcomes in the no IVT arm. Participant characteristics at randomization by time intervals from onset/last-seen-well to randomization were described using medians with IQR for continuous variables and proportions for discrete variables including all variables employed in any subsequent model.

The interaction was analyzed using logistic, linear or flexible parametric survival models for binary, continuous or time-to-event outcomes, respectively. For rare binary outcome, penalized maximum likelihood logistic regression (Firth method) was used. For the primary analysis, we analyzed the interaction term of the time interval (continuous variable)*IVT assignment. A linear relationship was used as default, but more flexible approaches (ie, fractional polynomials and linear splines) were also considered. For a secondary analysis, predefined time cut-offs were used with the rationale of the ‘golden hour’ for IVT (OTN 0–60 min vs 61–270 min),¹⁴ the Food and Drug Administration label for alteplase (0–180 min vs 181–270 min), and according to quartiles of OTN.¹⁵ Models were compared using Akaike and Bayesian information criteria. Interaction terms are reported with 95% confidence intervals (95% CI) and p values. Interpretation of p values of the interaction was based on the recommendations of the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) tool.¹⁶

Models were adjusted by the binary stratification variables and sex. Further covariate adjustments for baseline differences between early and late presenting patients were considered.

RESULTS

Cohort characteristics

Between November 2017 and May 2021, 423 patients at 42 centers were randomized and 15 patients were excluded after randomization. Altogether, 201 patients were assigned to MT alone and 207 to IVT+MT. The allocated intervention was received by 402/408 patients with three crossovers in each treatment arm. Data completeness was almost perfect for mRS (one missing) and >95% for all other outcomes (see online supplemental figure S1 for the CONSORT flow-chart). The median age was 72 years (IQR 64–81), 209 (51.2%) were female, and the median NIHSS was 17 (13–20). The median OTN was 135 min (IQR 107–176) and the median DTN was 53 min (IQR 40–69). The expected median OTN and DTN were 142 (112–177) min and 54 (40–69) min in the IVT+MT group, and 129 (106–170) min and 51 (41–67) min in the MT alone group.

Table 2 reports the baseline characteristics according to time delays of OTN; see online supplemental data table 1 for comparison according to DTN. Figure 1 depicts the distribution of time to treatment variables by randomization group.

Delay from onset (OTN)

We found no evidence that the effect of bridging IVT on functional independence was modified by the delay of OTN. The odds for functional independence in patients treated with alteplase plus thrombectomy versus thrombectomy alone numerically

Table 3 Interaction analysis regarding primary and secondary outcomes according to overall and in-hospital delays

Time	Outcome category	Outcome	aOR for MT alone per 1 hour delay with 95% CI	aOR of interaction per 1 hour delay with 95% CI*
Onset-to-needle* time: Expected time from symptom onset or last known well to IVT bolus	Efficacy	mRS 0–2 (primary), day 90	0.86, 0.60 to 1.23	0.76, 0.45 to 1.30
		mRS decrease (better outcome), day 90	0.82, 0.60 to 1.12	0.90, 0.58 to 1.39
		Mortality, day 90	1.57, 0.91 to 2.70	0.98, 0.42 to 2.32
	Safety	Any ICH on 24 hours imaging	1.35, 0.93 to 1.97	1.33, 0.78 to 2.27
		Symptomatic ICH on 24 hours imaging	1.15, 0.42 to 3.17	0.66, 0.17 to 2.65
	Pharmacological efficacy	Pre-interventional reperfusion success (cs-eTICI \geq 2a)	0.99, 0.40 to 2.42	1.56, 0.54 to 4.49
		Time-to-reperfusion	0.73, 0.60 to 0.89	1.24, 0.94 to 1.62,
		Final reperfusion success (cs-eTICI \geq 2b)	0.78, 0.44 to 1.37	1.04, 0.36 to 3.02
Door-to-needle* time: Expected time from arrival at the emergency department door to IVT bolus	Efficacy	mRS 0–2 (primary), day 90	1.47, 0.60 to 3.56	0.48, 0.14 to 1.62
		mRS decrease (better outcome), day 90	1.88, 0.91 to 3.88	0.36, 0.13 to 0.99
		Mortality, day 90	0.11, 0.02 to 0.66	17.8, 1.8 to 174.9
	Safety	Any ICH on 24 hours imaging	0.99, 0.40 to 2.43	0.95, 0.28 to 3.24
		Symptomatic ICH on 24 hours imaging	0.73, 0.05 to 10.74	4.60, 0.19 to 114.10
	Pharmacological efficacy	Pre-interventional reperfusion success (cs-eTICI \geq 2a)	2.26, 0.36 to 14.38	0.63, 0.07 to 6.06
		Time-to-reperfusion	0.40, 0.26 to 0.63	0.88, 0.47 to 1.64
		Final reperfusion success (cs-eTICI \geq 2b)	1.69, 0.37 to 7.81	0.56, 0.05 to 6.83

*The aOR indicates the interaction term of assignment to IVT+MT (as compared with MT alone) and 1 hour delay and group assignment assuming a linear effect. The OR for MT alone gives the change in the odds for functional independence per additional hour delay. The interaction refers to change in the treatment effect (odds for functional independence of IVT plus MT vs MT alone) per additional hour delay.

aOR, adjusted OR; cs-eTICI, cross-sectional expanded Thrombolysis In Cerebral Infarction; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; MT, mechanical thrombectomy.

decreased by 0.76 (95% CI 0.45 to 1.30, $p=0.32$) per hour of OTN delay. Similar results were obtained when assuming a dichotomous effect (adjusted odds ratio (aOR) of >3 hours vs 0–3 hours 0.64, 95% CI 0.24 to 1.72, $p=0.37$), across quartiles (see figure 2) or when using linear splines. Models fitted best when OTN was included as a linear effect and consistent with the sensitivity analysis using the individual times to IVT bolus administration (see online supplemental table S2).

There was no significant interaction of OTN and bridging IVT assignment in terms of the safety outcomes or the pharmacological and technical efficacy (see table 3).

In-hospital delay (DTN)

We also found no evidence that the effect of bridging IVT on functional independence is modified by the in-hospital delay. No heterogeneity was observed, including when assuming a dichotomous effect of DTN (aOR of >1 hour vs 0–1 hour 1.37, 95% CI 0.74 to 2.53). Similarly, across quartiles, there was no interaction of DTN and IVT assignment in terms of the primary outcome.

The adjusted odds for a favorable mRS shift numerically increased by 1.88 (95% CI 0.91 to 3.88) per 1 hour decrease of DTN resulting in a significant interaction with IVT assignment (aOR 0.36, 95% CI 0.13 to 0.99, $p=0.047$). In parallel, the mortality analysis (aOR 17.8, 95% CI 1.8 to 174.9, p for interaction 0.011) provided some evidence for a more beneficial effect of IVT when in-hospital delays were short (table 3).

DISCUSSION

This post-hoc analysis of the SWIFT-DIRECT trial found no clear evidence that patients with short OTN benefited more from bridging IVT. Exploratory analysis of secondary clinical outcomes indicated a potentially favorable effect of IVT associated with shorter in-hospital delays.

For patients qualifying for IVT without MT, earlier treatment is associated with increased proportional benefits, with potential harms only evident beyond the established 4.5 hour limit.¹⁷ For patients who received bridging IVT before MT, the randomized controlled trials on this topic have reported no clear subgroup effects related to the time from symptom onset to randomization. Also, our nuanced sub-analysis of the randomized SWIFT-DIRECT trial detected no heterogeneity of treatment effect. Our model fit was best when OTN was handled as a continuous variable (ie, assumption of a linear effect). The point estimate (aOR 0.76, 95% CI 0.45 to 1.30) crossed the zero effect line indicating potential harm at around 4 hours after symptom onset for the dichotomized functional independence and beyond 4 hours for the mRS shift analysis (aOR 0.90, 95% CI 0.58 to 1.39). Nevertheless, given the point estimates of all trials on this topic,^{5 6 18 19} the pathophysiology of ischemic stroke and IVT, as well as the low power of the subgroup analysis,¹⁵ it is possible that we missed a clinically important effect. Hence, this analysis should be repeated in an individual patient meta-analysis of comparable trials on bridging IVT.

No interaction could be detected with the secondary safety outcomes, and pharmacological and technical efficacy. However, a sub-analysis of the DEVT trial recently reported an association of bridging IVT with increased early reperfusion when MT was delayed more than approximately half an hour.²⁰

Analysis of in-hospital delays revealed a potential heterogeneity of treatment effect of IVT regarding mortality and mRS shift analysis, with a larger proportional benefit seen when DTN was shorter. However, the credibility of those subgroup effects is unclear because of multiple testing and hence, this finding might be due to chance.¹⁶ Nevertheless, since the anticipated direction of the effect and the pathophysiology support such heterogeneity, we suggest a re-analysis in an individual patient meta-analysis of the trials mentioned above. In a bigger dataset, potentially relevant subgroups such as tandem lesions should be specifically addressed.²

The meta-analysis of the trials on MT²¹ also found a time-to-treatment interaction for in-hospital delays, but not for overall delays from symptom onset. Possible reasons include a stronger association of in-hospital delays with outcome, the time-reset effect of imaging-based inclusion,²² uncertain trustworthiness of pre- versus in-hospital time workflow information, and non-linear ischemic core growth over time.^{23 24}

Strengths and limitations

Strengths include good overall data quality within the setting of the randomized prospective international multicenter SWIFT-DIRECT trial and a prespecified, deposited statistical analysis plan with defensive interpretation according to recommendations for subgroup analysis of randomized trials. Limitations are mainly related to the fact that the study was neither designed nor powered to detect an interaction effect—that is, assuming the observed correlations from the main study, odds ratios lower than 0.6 would be necessary to reach a power of 80%. Since imaging selection (ASPECTS) was used in the enrolled patients, the time effects observed are likely to be less pronounced than those that would occur in the overall population of patients with large-vessel occlusion in the absence of imaging selection.

CONCLUSIONS

This subgroup analysis found no evidence that the effect of bridging IVT on functional independence is modified by overall or in-hospital treatment delays. Considering the low statistical power of this subgroup analysis, a clinically important effect could have been missed. Nevertheless, exploratory analysis regarding secondary clinical outcomes indicated a potentially favorable effect of IVT associated with shorter in-hospital delays. Until further evidence regarding potential heterogeneity of the IVT effect size before MT becomes available from individual patient meta-analysis of comparable trials, IVT should be given to eligible patients and neither OTN nor DTN should influence treatment decisions regarding bridging IVT.

Author affiliations

¹Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland

²University Institute of Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland

³CTU Bern, University of Bern, Bern, Switzerland

⁴Department of Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

⁵Department of Neuroradiology, Hospices Civils de Lyon, Lyon, France

⁶Department of Diagnostic and Therapeutic Neuroradiology, Centre Hospitalier Universitaire de Toulouse, Toulouse, France

⁷Neuro Clinical Trial Unit, Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland

⁸Division of Neuroradiology and Division of Neurosurgery, Departments of Medical Imaging and Surgery, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada

⁹Department of Neurology, Centre Hospitalier Universitaire de Toulouse, Toulouse, France

¹⁰Department of Diagnostic and Interventional Neuroradiology, Centre Hospitalier Universitaire de Nantes, Nantes Université, Nantes, France

¹¹Department of Neurology, Centre Hospitalier Universitaire de Nantes, Nantes Université, Nantes, France

¹²Department of Radiology, CHU Rouen, Rouen, France

¹³Department of Neurology, CHU Rouen, Rouen, France

¹⁴Department of Diagnostic and Therapeutic Neuroradiology, CHRU-Nancy, Université de Lorraine, INSERM U1254, Nancy, France

¹⁵Department of Neurology, Stroke Unit, CHRU-Nancy, Université de Lorraine, INSERM U1116, Nancy, France

¹⁶Department of Neurology, Klinikum Nürnberg, Nürnberg, Germany

¹⁷Department of Diagnostic and Interventional Neuroradiology, University Medical Center Göttingen, Göttingen, Germany

¹⁸Department of Neurology, CHU Caen Normandie, University Caen Normandie, INSERM U1237, Caen, France

¹⁹Department of Neuroradiology, CHU Caen Normandie, University Caen Normandie, INSERM U1237, Caen, France

²⁰Department of Vascular Neurology, Hospices Civils de Lyon, Lyon, France

²¹Department of Neurology, St George's University Hospital NHS Foundation Trust, London, UK

²²Department of Interventional and Diagnostic Neuroradiology, CHU Bordeaux, University of Bordeaux, Bordeaux, France

²³Stroke Unit, CHU Bordeaux, University of Bordeaux, Bordeaux, France

²⁴Department of Neuroradiology, University Hospital RWTH Aachen, Aachen, Germany

²⁵Department of Neurology, University Hospital RWTH Aachen, Aachen, Germany

²⁶Department of Stroke and Diagnostic and Interventional Neuroradiology, Foch Hospital, Suresnes, France

²⁷Stroke Unit, Department of Neurology, Hospital Vall d'Hebron, Barcelona, Spain

²⁸Interventional Neuroradiology, Department of Radiology, Hospital Vall d'Hebron, Barcelona, Spain

²⁹Department of Neuroradiology, CHU Limoges, Limoges, France

³⁰Department of Neurology, CHU Reims, Reims, France

³¹Department of Neuroradiology, CHU Reims, Reims, France

³²Service of Interventional and Diagnostic Radiology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland

³³Department of Neurology, Hôpitaux Universitaires de Genève, Geneva, Switzerland

³⁴Department of Diagnostic and Interventional Neuroradiology, Tours University Hospital, Tours, France

³⁵Stroke Unit, Department of Neurosciences, University Hospital Germans Trias i Pujol, Barcelona, Spain

³⁶Department of Interventional Neuroradiology, Strasbourg University Hospitals, Strasbourg, France

³⁷Department of Neurology, Lille University Hospital, Lille, France

³⁸Department of Neurology, University Hospital Zurich, Zurich, Switzerland

³⁹Department of Neurology, Cereneo, Center for Neurology and Rehabilitation, Vitznau, Switzerland

⁴⁰Department of interventional Neuroradiology, Fondation Rothschild Hospital, Paris, France

⁴¹Department of Neuroradiology, Brest University Hospital, Brest, France

⁴²Department of Neurology, University Health Network - Toronto Western Hospital - University of Toronto, Toronto, Ontario, Canada

⁴³Department of Neurology, University Hospital Frankfurt, Frankfurt, Germany

⁴⁴Department of Neurosurgery, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, New York, USA

⁴⁵Vanderbilt Cerebrovascular Program, Vanderbilt University Medical Center, Nashville, Tennessee, USA

⁴⁶School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA

⁴⁷Department of Intracranial Endovascular Therapy, Alfried-Krupp Krankenhaus, Essen, Germany

⁴⁸Department of Neuroradiology, Hôpitaux Universitaires de Genève, Geneva, Switzerland

⁴⁹Department of Neuroepidemiology, Institute for Medical Informatics, Biometry and Epidemiology (IMIBE), Essen, Germany

⁵⁰Department of Neuroradiology, University Hospital of Zurich, Zurich, Switzerland

⁵¹Department of Neurology, University Hospital Basel, Basel, Switzerland

⁵²Department of Neurology and Comprehensive Stroke Center, David Geffen School of Medicine, UCLA, University of California, Los Angeles, California, USA

Twitter Thomas R Meinel @TotoMynell, Johannes Kaesmacher @CheesemakerMD, Vitor Mendes Pereira @VitorMendesPer1, Raoul Pop @RaoulPop25 and Urs Fischer @FishingNeurons

Acknowledgements Academic investigators designed SWIFT-DIRECT. Susan Kaplan provided English language support.

Collaborators List of SWIFT DIRECT Study Personnel, Collaborators and Affiliations
Principal Investigators: Urs Fischer MD, MSc1,2, Jan Gralla MD, MSc3 Steering Board Rene Chapot MD4, Christoph Cognard MD5, Urs Fischer MD MSc1,2, Anthony Furlan MD6, Michael T Froehler MD PhD7, Jan Gralla MD MSc3, Vitor Mendes-Pereira MD PhD8, Jeffrey L Saver MD9, Adnan H. Siddiqui MD PhD10, Daniel Strbian MD PhD11, Martin Wiesmann MD12 Study Management Sandro Deppeler MSc13, Patricia Plattner MSc13, Melanie Schmidhalter MSc13, Jenny Bressan MSc13, Stefania Lerch PhD13 PhD Student Johannes Kaesmacher MD3 Independent trial statisticians Lukas Bütikofer PhD14, Andreas Limacher PhD14 Study monitors Leonhard von Meyenn PhD14, Martina Zimmermann PhD14 Data Safety Monitoring Board Bruce Campbell MD PhD15, Tim Friede PhD16, Rüdiger von Kummer MD17 Clinical Event Committee Leo Bonati MD2, Hans Christoph Diener MD18, Paolo Machi MD19, Zsolt Kulcsar MD PhD20 Imaging Core Lab David S. Liebeskind MD9 Collaborators Angelika Alonso MD21, Caroline Arquizan MD22, Xavier Barreau MD23, Rémy Beaujeux MD PhD24, Daniel Behme MD25, Tobias Boeckh-Behrens MD26, Christian Boehme MD PhD27, Marti Boix MSc28, Grégoire Boulois MD PhD29, Nicolas Bricout MD30, Nicolas Broc MD31, Carlo W. Cereda MD32, Emmanuel Chabert MD33, Tae-Hee Cho MD PhD34, Alessandro Cianfoni MD3,35, Vincent Costalat MD PhD36, Christian Denier MD PhD37, Federico Di Maria MD38, Richard du Mesnil de Rochemont MD39, Patricia Fearon MD40, Anna Ferrier MD41, Sebastian Fischer MD42, Maxime Gauberti MD PhD43, Marie Gaudron MD44, Laetitia Gimenez MD4, Christoph Globas MD46, Michael Görtler MD PhD47, Mayank Goyal MD PhD48, Ruediger HilkerRoggendorf MD PhD49, Michael D. Hill MD MSc50, Vi Tuan Hua MD51, Lisa Humbertjean MD52, Olav Jansen MD PhD53, Simon Jung MD1, Georg Kägi54, Michael E. Kelly MD PhD55, Ilka Kleffner MD56, Michael Knoflach 4 MD27, Nedeltchev Krassen MD1, 57, Lars Udo Krause MD58, Kimmo Lappalainen MD59, Margaux Lefebvre MD60, Joe Leyon MD MBA61, Liang Liao MD62, Jean-Sebastien Lieghey MD63, Christian Loehr MD64, Patrik Patrik MD65, Stefania Nannoni MD PhD65, Patrick Nicholson MD8, Lorena Nico MD66, Michael Obadia MD67, Julien Ognard MD PhD68, Ayokunle Ogungbemi MD MBS61, Jean-Marc Olivot MD PhD69, Simon Escalard MD70, Marco Pasi MD PhD71, Lissa Peeling MD55, Jane Perez MD72, Martina Petersen MD58, Eike Piechowiak MD3, Roberto Raposo MD PhD69, Silja Rätty MD PhD11, Sarah C. Reitz MD73, Sebastia Remollo MD74, Luca Remonda MD3,75, Ian Rennie MD76, Manuel Requena MD77, Alexander Riabikin12, Roberto Riva MD78, Aymeric Rouchaud MD PhD79, Andrea Rosi MD19, Marta Rubiera MD80, Laurent Spelle MD PhD81, Marlina Schnieder MD82, Joanna D. Schaafsma MD PhD83, Tilman Schubert20,84, Jörg B Schulz MD85,86, Mohammed Siddiqui MD72, Sébastien Soize MD MSc8, Michael Sonnberger MD88, Emmanuel Touze MD PhD89, Aude Triquetnot MD90, Guillaume Turc MD PhD91, Lucy Vieira MD92, Ben Hassen Wagih MD PhD93, Judith N. Wagner MD94, Katrin Wasser MD81, Johannes Weber95, Holger Wenz MD96, David Weisenburger-Lile MD38, Fritz Wodarg MD53, Valérie Wolff MD PhD97, Silke Wunderlich MD98Affiliations 1 Department of Neurology, University Hospital Bern, Inselspital, University of Bern, Bern, Switzerland. 2 Department of Neurology, University Hospital Basel, University of Basel, Basel, Switzerland. 3 University Institute of Diagnostic and Interventional Neuroradiology, University Hospital Bern, Inselspital, University of Bern, Bern, Switzerland. 4 Department of Intracranial Endovascular Therapy, Alfried Krupp Krankenhaus Essen, Essen, Germany. 5 Department of Diagnostic and Therapeutic Neuroradiology, Centre Hospitalier Universitaire de Toulouse, Toulouse, France. 6 School of Medicine, Case Western Reserve University, Cleveland, OH, USA. 7 Vanderbilt Cerebrovascular Program, Vanderbilt University Medical Center, Nashville, USA. 8 Division of Neuroradiology and Division of Neurosurgery, Departments of Medical Imaging and Surgery, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Canada. 9 Department of Neurology and Comprehensive Stroke Center, David Geffen School of Medicine, University of California, Los Angeles, USA. 10 Department of Neurosurgery, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, New York, USA. 11 Department of Neurology, Helsinki University Hospital and University of Helsinki, Finland. 12 Department of Neuroradiology, University Hospital RWTH Aachen, Aachen, Germany. 13 Neuro Clinical Trial Unit, Department of Neurology, University Hospital Bern, Inselspital, University of Bern, Bern, Switzerland. 14 CTU Bern, University of Bern, Bern, Switzerland. 15 Departments of Medicine and Neurology, Melbourne Brain Centre at The Royal Melbourne Hospital, and the Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia 16 Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany. 17 Institute and Policlinic of Diagnostic and Interventional Neuroradiology, Universitätsklinikum Dresden, Dresden, Germany. 18 Department of Neuroepidemiology, Institute for Medical Informatics, Biometry and Epidemiology

(IMIBE), Essen, Germany. 19 Department of Neuroradiology, Hôpitaux Universitaires de Genève, Geneva, Switzerland. 20 Department of Neuroradiology, University Hospital of Zurich, Zurich, Switzerland. 21 Department of Neurology, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany. 22 Department of Neurology, Montpellier University Hospital, Montpellier, France. 23 Department of Diagnostic and Therapeutic Neuroradiology, CHU de Bordeaux, Bordeaux, France. 24 Department of Interventional Neuroradiology, University Hospital Strasbourg, Strasbourg, France. 25 Clinic for Neuroradiology, University Medical Center Magdeburg, Magdeburg, Germany. 26 Department of Neuroradiology, School of Medicine, University Hospital Rechts der Isar of the Technical University Munich, Munich, Germany. 27 Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria. 28 Department of Neurosciences, University Hospital Germans Trias i Pujol, Barcelona, Spain. 29 Diagnostic and Interventional Neuroradiology, Tours University Hospital, INSERM 1253 iBRAIN, Tours, France. 30 Department of Interventional Neuroradiology, Centre Hospitalier Regional Universitaire de Lille, Lille, France. 31 Department of Neurology, Geneva University Hospitals, Geneva, Switzerland. 32 Stroke Center, Neurology, Neurocenter of Southern Switzerland – EOC, Lugano, Switzerland. 33 Neuroradiology Department, Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France. 34 Department of Vascular Neurology, Hospices Civils de Lyon, Lyon, France. 35 Department of Neuroradiology, Neurocenter of Southern Switzerland – EOC, Lugano, Switzerland. 36 Department of Neuroradiology, Montpellier University Hospital, Montpellier, France. 37 Department of Neurology, Hopital Bicetre, APHP, Paris Sud Université, Paris, France. 38 Department of Stroke and Diagnostic and Interventional Neuroradiology, Foch Hospital, Suresnes, France. 39 Department of Neuroradiology, University Hospital Frankfurt, Goethe-University, Frankfurt, Germany. 40 Department of Stroke Medicine, Royal Victoria Hospital, Belfast, UK. 41 Neurology Department, Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France. 42 Department of Diagnostic and Interventional Neuroradiology and Nuclear Medicine, University Hospital Knappschaftskrankenhaus Bochum, Universitätsklinik der Ruhr-Universität, Bochum, Germany. 43 Neuroradiology Department, CHU Caen Normandie, INSERM U1237, University Caen Normandie, Caen, France. 44 Stroke Unit, Tours University Hospital, Tours, France. 45 Neurology Department, University Hospital of Limoges, Limoges, France. 46 Department of Neurology, University Hospital of Zurich, Zurich, Switzerland. 47 Clinic for Neurology, University Medical Center Magdeburg, Magdeburg, Germany. 48 Department of Radiology, University of Calgary, Foothills Hospital, Calgary, Canada. 49 Department of Neurology, Klinikum Vest, Recklinghausen, Germany. 50 Department of Clinical Neurosciences, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Foothills Hospital, Calgary, Canada. 51 Department of Neurology, CHU Reims, Reims, France. 52 Department of Neurology, CHRU-Nancy, Université de Lorraine, Nancy, France. 53 Department of Radiology and Neuroradiology, University Hospital Kiel, Kiel, Germany. 54 Department of Neurology, Cantonal Hospital St. Gallen, St.Gallen, Switzerland. 55 Division of Neurosurgery, University of Saskatchewan, Saskatoon, Canada. 56 Department of Neurology, University Hospital Bochum, Bochum, Germany. 57 Department of Neurology, Cantonal Hospital of Aarau, Aarau, Switzerland. 58 Department of Neurology, Klinikum Osnabrück, Osnabrück, Germany. 59 Medical Imaging Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland 60 Department of Radiology, CHU Rouen, Rouen, France. 61 Department of Neuroradiology, St George's University Hospital, London, UK 62 Department of Neuroradiology, CHRU-Nancy, Université de Lorraine, Nancy, France. 63 Stroke Unit, Bordeaux University Hospital, Bordeaux, France. 64 Department of Neuroradiology, Klinikum Vest, Recklinghausen, Germany 65 Stroke Center, Service of Neurology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland 66 Department of Neuroradiology, CHU Saint Étienne, Saint-Priest-en-Jarez, France. 67 Department of Neurology, Fondation Rothschild Hospital, Paris, France. 68 Diagnostic and Interventional Neuroradiology, Brest University Hospital, Brest, France. 69 Department of Neurology, Centre Hospitalier Universitaire de Toulouse, Toulouse. 70 Department of Neuroradiology, Fondation Rothschild Hospital, Paris, France. 71 Department of Neurology, Centre Hospitalier Regional Universitaire de Lille, Lille, France. 72 Department of Neurology, Salford Royal NHS Foundation Trust, Manchester, UK. 73 Department of Neurology, University Hospital Frankfurt, Goethe-University, Frankfurt, Germany. 74 Department of Interventional Neuroradiology, University Hospital Germans Trias i Pujol, Barcelona, Spain. 75 Department of Neuroradiology, Cantonal Hospital Aarau, Aarau, Switzerland. 76 Department of Interventional Neuroradiology, Royal Victoria Hospital, Belfast, UK. 77 Department of Interventional Neuroradiology, Hospital Vall d'Hebron, Barcelona, Spain. 78 Department of Neuroradiology, Hospices Civils de Lyon, Lyon, France. 79 Department of Neuroradiology, University Hospital of Limoges, Limoges, France. 80 Department of Neurology, Hospital Vall d'Hebron, Barcelona, Spain. 81

Department of Neuroradiology, Hôpital Bicêtre, APHP, Paris Sud Université, Paris, France. 82 Department of Neurology, University Medical Center Goettingen, Goettingen, Germany. 83 Department of Neurology, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Canada. 84 Clinical Neurocenter, University Hospital of Zurich, Zurich, Switzerland. 85 Department of Neurology, University Hospital RWTH Aachen, Aachen, Germany. 86 JARA-BRAIN Institute Molecular Neuroscience and Neuroimaging, Forschungszentrum Jülich GmbH, RWTH Aachen University, Aachen, Germany. 87 Department of Neuroradiology, CHU Reims, Reims, France. 88 Department of Neuroradiology, Kepler University Hospital, Linz, Austria. 89 Department of Neurology, CHU Caen Normandie, INSERM U1237, University Caen Normandie, Caen, France. 90 Department of Neurology, CHU Rouen, Rouen, France. 91 Department of Neurology, GHU Paris Psychiatrie et Neurosciences & Université de Paris & INSERM U1266 & FHU NeuroVasc, Paris, France. 92 Montreal Neurological Hospital, McGill University Health Center, Montreal, Canada. 93 Department of neuroradiology, GHU Paris Psychiatrie et Neurosciences & Université de Paris & INSERM U1266 & FHU NeuroVasc, Paris, France. 94 Department of Neurology, Kepler University Hospital, Linz, Austria. 95 Department of Radiology and Nuclear Medicine, Kantonsspital St Gallen, Sankt Gallen, Switzerland. 96 Department of Neuroradiology, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany. 97 Department of Neurology, University Hospital Strasbourg, Strasbourg, France. 98 Department of Neurology, School of Medicine, University Hospital Rechts der Isar of the Technical University Munich, Munich, Germany.

Contributors TM, JK, LB, JG and UF contributed to conception and design of the study, analysis of data and drafting the text. TRM, JK and LB performed the statistical analysis and prepared the figures. All co-authors contributed to acquisition of data, provided significant input to interpretation of data and reviewed the paper and revised it for important intellectual content. UF and JG are the guarantors of this work.

Funding Medtronic supported the study with an unrestricted grant to the University Hospital Bern. Medtronic had no involvement in the final design, data analysis or interpretation. The University Hospital of Bern provided additional funding.

Competing interests MA reports honoraria for lectures from AstraZeneca, Bayer, Covidien, Medtronic and Sanofi; Participation on Scientific Advisory Boards of Amgen, Bayer, BMS, Daiichi Sankyo, Medtronic, and Pfizer. CC reports consulting fees from Medtronic (payment made to CC). EC reports grants from the Swiss Heart Foundation and Swiss National Science Foundation, not related to present study. HCD reports that in the last 3 years, he received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, BMS, Boehringer Ingelheim, Daiichi Sankyo, Novo-Nordisk, Pfizer, Portola and WebMD Global. Boehringer Ingelheim provided financial support for research projects. HCD also received research grants from the German Research Council (DFG) and German Ministry of Education and Research (BMBF). HCD serves as editor of *Neurologie up2date*, *Info Neurologie & Psychiatrie*, *Arzneimitteltherapie*, as co-editor of *Cephalalgia* and on the editorial board of *Lancet Neurology* and *Drugs*. MTF reports research grants from Medtronic, Siemens, Genentech, Idorsia, and Vesalio; consulting fees from Genentech, Balt USA, Cerenovus, and Oculus Imaging; participation on a Data Safety Monitoring Board or Advisory Board for Balt USA, Jacobs Institute, and Imperative Care. UF reports financial support for the present study from Medtronic. SWIFT DIRECT is an investigator-initiated trial. The sponsor was not involved in the final study design, protocol, conduct, evaluation of results or preparation of the manuscript. UF also reports research grants from Medtronic BEYOND SWIFT registry, Swiss National Science Foundation, Swiss Heart Foundation; consulting fees from Medtronic, Stryker and CSL Behring (fees paid to institution); membership of a Data Safety Monitoring Board for the IN EXTREMIS trial and TITAN trial and Portola (Alexion) Advisory board (fees paid to institution); and Vice Presidency of the Swiss Neurological Society. UF is a member of the editorial board of *JNIS*. JG reports a Swiss National Funds (SNF) grant for MRI in stroke. JK reports financial support of Medtronic for the BEYOND SWIFT Registry (fees paid to institution); research grant from the Swiss National Science Foundation supporting the TECNO trial (fees paid to institution); Swiss Academy of Medical Sciences research grant supporting MRI research (fees paid to institution); Swiss Heart Foundation research grant supporting cardiac MRI in the etiological workup of stroke patients (fees paid to institution). AL reports grants from the University of Zurich, the LOOP Zurich, and P&K Pühringer Foundation; consulting fees from Bayer AG; and a lecture honorarium from Moleac Pte, Singapore. DSL reports consulting fees from Cerenovus, Genentech, Medtronic, Stryker, Rapid Medical as imaging core lab. GM reports consulting fees from Stryker Neurovascular; paid lectures for Medtronic and Microvention Europe. PM reports research funding (fees paid to institution) from the Swiss National Science Foundation, Swiss Heart Foundation and Medtronic Research Grant. PM reports grants from the Swiss National Science Foundation; Consulting fees Medtronic, Stryker; payment or honoraria from Medtronic, Stryker; participation on a Data Safety Monitoring Board or Advisory Board of Microvention. ON reports funding from a Stryker Research grant; payment or honoraria for Phenox lecture and Stryker lecture.

WP reports grants from the German Research Foundation, LOEWE (research funding of the federal state of Hesse); royalties or licenses STROKE TEAM-Training (LAERDAL medical); payment or honoraria from LAERDAL medical, Alexion, Pfizer-BMS, Stryker Neurovascular; support for attending meetings and/or travel from LAERDAL medical, Alexion, Pfizer-BMS and Stryker Neurovascular. MR reports consulting fees from Medtronic, Stryker, Cerenovus, Phillips and Apta Targets; payment or honoraria from Ischemia View; participation on a Data Safety Monitoring Board or Advisory Board of Somsome; stock or stock options in Anaconda Biomed, CVAid and Methinks. AHS reports being a co-investigator for NIH - 1R01EB030092-01, Project Title: High Speed Angiography at 1000 frames per second; Mentor for Brain Aneurysm Foundation Carol W. Harvey Chair of Research, Sharon Epperson Chair of Research, Project Title: A Whole Blood RNA Diagnostic for Unruptured Brain Aneurysm: Risk Assessment Prototype Development and Testing; receipt of consulting fees from Amnis Therapeutics, Apellis Pharmaceuticals, Inc, Boston Scientific, Canon Medical Systems USA, Inc, Cardinal Health 200, LLC, Cerebrotech Medical Systems, Inc, Cerenovus, Cerevatech Medical, Inc, Cordis, Corindus, Inc, Endostream Medical, Ltd, Imperative Care, InspireMD, Ltd, Integra, IRRAS AB, Medtronic, Microvention, Minnetronix Neuro, Inc, Peijia Medical, Penumbra, Q'Apel Medical, Inc, Rapid Medical, Serenity Medical, Inc, Silk Road Medical, StimMed, LLC, Stryker Neurovascular, Three Rivers Medical, Inc, VasSol, Viz.ai, Inc (payments made to AHS); Secretary – Board of the Society of NeuroInterventional Surgery 2020-2021 (unpaid) Chair – Cerebrovascular Section of the AANS/CNS 2020-2021 (unpaid); stock or stock options Adona Medical, Inc, Amnis Therapeutics, Bend IT Technologies, Ltd, BlinkTBI, Inc, Cerebrotech Medical Systems, Inc, Cerevatech Medical, Inc, Cognition Medical, CVAID Ltd, E8, Inc, Endostream Medical, Ltd, Galaxy Therapeutics, Inc, Imperative Care, Inc, InspireMD, Ltd, Instylla, Inc, International Medical Distribution Partners, Launch NY, Inc, NeuroRadial Technologies, Inc, NeuroTechnology Investors, Neurovascular Diagnostics, Inc, Peijia Medical, PerFlow Medical, Ltd, Q'Apel Medical, Inc, QAS.ai, Inc, Radical Catheter Technologies, Inc, Rebound Therapeutics Corp (purchased 2019 by Integra Lifesciences, Corp), Rist Neurovascular, Inc (Purchased 2020 by Medtronic), Sense Diagnostics, Inc, Serenity Medical, Inc, Silk Road Medical, Sim & Cure, SongBird Therapy, Spinnaker Medical, Inc, StimMed, LLC, Synchron, Inc, Three Rivers Medical, Inc, Truvis Medical, Inc, Tulavi Therapeutics, Inc, Vastrax, LLC, VICIS, Inc, Viseon, Inc (payments made to AHS); Other financial or non-financial interests: National PI/Steering Committees: Cerenovus EXCELLENT and ARISE II Trial; Medtronic SWIFT PRIME, VANTAGE, EMBOLISE and SWIFT DIRECT Trials; Microvention FRED Trial & CONFIDENCE Study; MUSC POSITIVE Trial; Penumbra 3D Separator Trial, COMPASS Trial, INVEST Trial, MIVI neuroscience EVAQ Trial; Rapid Medical SUCCESS Trial; InspireMD C-GUARDIANS IDE Pivotal Trial (payments made to AHS). IS reports consulting fees (paid to IS) from Sanofi Synthé-Labo, Servier, Boehringer Ingelheim, AstraZeneca, Novonordisk and Medtronic; payment or honoraria (paid to IS) from Sanofi Synthé-Labo, Medtronic, Boehringer Ingelheim, AstraZeneca and BMS-Pfizer. JS reports funding for the present manuscript from Medtronic (paid to JS); consulting fees from Cerenovus (paid to JS); participation on a Data Safety Monitoring Board or Advisory Board – MIVI (paid to JS), Phillips (paid to JS); stock or stock options in Rapid Medical (paid to JS). MW reports a grant from Stryker Neurovascular; consulting fees from Stryker Neurovascular (payments to MW); payment or honoraria from Stryker Neurovascular, Bracco Imaging (payments to MW); German Society of Neuroradiology (DGNR) Board member (no payments); receipt of equipment, materials, drugs, medical writing, gifts or other services from ab medica, Acandis, Bracco Imaging, Cerenovus, Kaneka Pharmaceuticals, Medtronic, Mentice AB, Phenox, Stryker Neurovascular (support to institution). All other authors report no competing interests.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Bern Ethics Committee KEK-2021. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. De-identified data, together with a data dictionary, will be made accessible after ethics clearance and upon submission of a reasonable request with a research plan to the corresponding author.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is

properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Thomas R Meinel <http://orcid.org/0000-0002-0647-9273>
 Johannes Kaesmacher <http://orcid.org/0000-0002-9177-2289>
 Christophe Cognard <http://orcid.org/0000-0003-4287-2627>
 Vitor Mendes Pereira <http://orcid.org/0000-0002-6804-3985>
 Jean Darcourt <http://orcid.org/0000-0003-1620-4449>
 Chrysanthi Papagiannaki <http://orcid.org/0000-0002-9473-9644>
 Sébastien Richard <http://orcid.org/0000-0002-0945-5656>
 Laura Mechtouff <http://orcid.org/0000-0001-9165-5763>
 Gaultier Marnat <http://orcid.org/0000-0002-7611-7753>
 Omid Nikoubashman <http://orcid.org/0000-0002-2055-4217>
 Manuel Requena <http://orcid.org/0000-0002-5671-6484>
 Alvaro Garcia-Tornel <http://orcid.org/0000-0003-3633-3002>
 Paolo Pagano <http://orcid.org/0000-0001-5821-2653>
 Guillaume Saliou <http://orcid.org/0000-0003-3832-7976>
 Kevin Janot <http://orcid.org/0000-0002-7305-3125>
 Raoul Pop <http://orcid.org/0000-0003-4417-1496>
 Martin Wiesmann <http://orcid.org/0000-0002-8261-5513>
 David Liebeskind <http://orcid.org/0000-0002-5109-8736>
 Jeffrey L Saver <http://orcid.org/0000-0001-9141-2251>

REFERENCES

- Lin C-H, Saver JL, Ovbiagele B, et al. Endovascular thrombectomy without versus with intravenous thrombolysis in acute ischemic stroke: a non-inferiority meta-analysis of randomized clinical trials. *J Neurointerv Surg* 2022;14:227–32.
- Anadani M, Marnat G, Consoli A, et al. Endovascular therapy with or without intravenous thrombolysis in acute stroke with tandem occlusion. *J Neurointerv Surg* 2022;14:314–20.
- Zi W, Qiu Z, Li F, et al. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke. *JAMA* 2021;325:234–43.
- Yang P, Zhang Y, Zhang L, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;382:1981–93.
- LeCouffe NE, Kappelhof M, Treurniet KM, et al. A randomized trial of intravenous alteplase before endovascular treatment for stroke. *N Engl J Med* 2021;385:1833–44.
- Suzuki K, Matsumaru Y, Takeuchi M, et al. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA* 2021;325:244–53.
- Fischer U, Kaesmacher J, Strbian D, et al. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. *Lancet* 2022;400:104–15.
- Kaesmacher J, Mujanovic A, Treurniet K, et al. Perceived acceptable uncertainty regarding comparability of endovascular treatment alone versus intravenous thrombolysis plus endovascular treatment. *J Neurointerv Surg* 2022. doi:10.1136/neurintsurg-2022-018665. [Epub ahead of print: 01 Mar 2022].
- Turc G, Tsvigoulis G, Audebert HJ, et al. European Stroke Organisation – European Society for Minimally Invasive Neurological Therapy expedited recommendation on indication for intravenous thrombolysis before mechanical thrombectomy in patients with acute ischaemic stroke and anterior circulation large vessel occlusion. *Eur Stroke J* 2022;7:1–XXVI.
- Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014;384:1929–35.
- Fischer U, Kaesmacher J, Plattner P S. SWIFT DIRECT: Solitaire™ with the intention for thrombectomy plus intravenous t-PA versus DIRECT Solitaire™ stent-retriever thrombectomy in acute anterior circulation stroke: methodology of a randomized, controlled, multicentre study. *Int J Stroke* 2021;0:1–8.
- Meinel TR, Fischer U, Bütikofer L. Data analysis plan. Available: <https://osf.io/4npxr/>
- Liebeskind DS, Bracard S, Guillemin F, et al. eTICI reperfusion: defining success in endovascular stroke therapy. *J Neurointerv Surg* 2019;11:433–8.
- Ebinger M, Kunz A, Wendt M, et al. Effects of golden hour thrombolysis: a prehospital acute neurological treatment and optimization of medical care in stroke (PHANTOM-S) substudy. *JAMA Neurol* 2015;72:25–30.
- Kent DM, Steyerberg E, van Klaveren D. Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects. *BMJ* 2018;363:k4245.
- Schandelmaier S, Briel M, Varadhan R, et al. Development of the instrument to assess the credibility of effect modification analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ* 2020;192:E901–6.
- Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014;384:1929–35.
- Yang P, Zhang Y, Zhang L, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;382:1981–93.
- Zi W, Qiu Z, Li F, et al. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA* 2021;325:234–43.
- Zhou Y, Zhang L, Ospel J, et al. Association of intravenous alteplase, early reperfusion, and clinical outcome in patients with large vessel occlusion stroke: post hoc analysis of the randomized DIRECT-MT trial. *Stroke* 2022;53:1828–36.
- Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA* 2016;316:1279–88.
- Fiehler J. The time-reset effect: thrombectomy trials challenge the existence of a time window. *Clin Neuroradiol* 2017;27:3–5.
- Saver JL. Time is brain—quantified. *Stroke* 2006;37:263–6.
- Jung S, Gilgen M, Slotboom J, et al. Factors that determine penumbral tissue loss in acute ischaemic stroke. *Brain* 2013;136:3554–60.