Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial

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Summary

Background Whether thrombectomy alone is equally as effective as intravenous alteplase plus thrombectomy remains controversial. We aimed to determine whether thrombectomy alone would be non-inferior to intravenous alteplase plus thrombectomy in patients presenting with acute ischaemic stroke.

Methods In this multicentre, randomised, open-label, blinded-outcome trial in Europe and Canada, we recruited patients with stroke due to large vessel occlusion confirmed with CT or magnetic resonance angiography admitted to endovascular centres. Patients were randomly assigned (1:1) via a centralised web server using a deterministic minimisation method to receive stent-retriever thrombectomy alone or intravenous alteplase plus stent-retriever thrombectomy. In both groups, thrombectomy was initiated as fast as possible with any commercially available Solitaire stent-retriever revascularisation device (Medtronic, Irvine, CA, USA). In the combined treatment group, intravenous alteplase (0·9 mg/kg bodyweight, maximum dose 90 mg per patient) was administered as early as possible after randomisation for 60 min with 10% of the calculated dose given as an initial bolus. Personnel assessing the primary outcome were masked to group allocation; patients and treating physicians were not. The primary binary outcome was a score of 2 or less on the modified Rankin scale at 90 days. We assessed the non-inferiority of thrombectomy alone versus intravenous alteplase plus thrombectomy in all randomly assigned and consenting patients using the one-sided lower 95% confidence limit of the Mantel-Haenszel risk difference, with a prespecified non-inferiority margin of 12%. The main safety endpoint was symptomatic intracranial haemorrhage assessed in all randomly assigned and consenting participants. This trial is registered with ClinicalTrials.gov, NCT03192332, and is closed to new participants.

Findings Between Nov 29, 2017, and May 7, 2021, 5215 patients were screened and 423 were randomly assigned, of whom 408 (201 thrombectomy alone, 207 intravenous alteplase plus thrombectomy) were included in the primary efficacy analysis. A modified Rankin scale score of 0–2 at 90 days was reached by 114 (57%) of 201 patients assigned to thrombectomy alone and 135 (65%) of 207 patients assigned to intravenous alteplase plus thrombectomy (adjusted risk difference –7·3%, 95% CI –16·6 to 2·1, lower limit of one-sided 95% CI –15·1%, crossing the non-inferiority margin of –12%). Symptomatic intracranial haemorrhage occurred in five (2%) of 201 patients undergoing thrombectomy alone and seven (3%) of 202 patients receiving intravenous alteplase plus thrombectomy (risk difference –1·0%, 95% CI –4·8 to 2·7). Successful reperfusion was less common in patients assigned to thrombectomy alone (182 [91%] of 201 *vs* 199 [96%] of 207, risk difference –5·1%, 95% CI –10·2 to 0·0, p=0·047).

Interpretation Thrombectomy alone was not shown to be non-inferior to intravenous alteplase plus thrombectomy and resulted in decreased reperfusion rates. These results do not support omitting intravenous alteplase before thrombectomy in eligible patients.

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Research in context

Evidence before this study

Whether thrombectomy alone is equally as effective as intravenous alteplase plus thrombectomy in patients with acute stroke due to large vessel occlusion admitted to centres with endovascular facilities remains controversial. We searched PubMed for randomised controlled trials published in English from Jan 1, 2010, to Jan 2, 2022, which compared thrombectomy alone with intravenous alteplase plus thrombectomy in patients with acute stroke. The following search terms were used: "stroke" AND ("thrombectomy" OR "mechanical" OR "endovascular" OR "aspiration" OR "stent-retriever") AND ("alteplase" OR "rtpa" OR "thrombolysis" OR "bridging"). Four randomised controlled trials met the criteria. Two trials from China (DIRECT-MT and DEVT) found that, given the selected non-inferiority margins, thrombectomy alone was non-inferior to alteplase followed by thrombectomy, whereas a trial from Japan (SKIP) and a trial from Europe (MR CLEAN-NO IV) could not show non-inferiority. There was considerable between-study heterogeneity regarding patient population, stroke aetiology, and workflow organisation, which might explain why some trials formally showed non-inferiority, whereas others failed to do so.

A formal study-level meta-analysis of the above-mentioned trials concluded that thrombectomy alone is non-inferior to intravenous alteplase plus thrombectomy at several non-inferiority margins proposed in the literature (up to −5%), but did not meet the most conservative, survey-derived margin of −1·3%. Hence, there is considerable uncertainty as to whether thrombectomy alone can be regarded as equally as effective and safe as intravenous alteplase plus thrombectomy, especially as there is a paucity of data in patients from Europe and North America.

Added value of this study

The SWIFT DIRECT trial could not show non-inferiority of thrombectomy alone considering a liberal non-inferiority margin of −12%. Despite strict inclusion and exclusion criteria aimed at studying a population most likely to benefit from thrombectomy alone, point estimates directionally favoured intravenous alteplase plus thrombectomy. Although alteplase-associated preinterventional reperfusion occurred infrequently, final postinterventional reperfusion rates were higher in patients assigned to intravenous alteplase plus thrombectomy, a significant difference not reported previously and a likely reason for the favourable outcome shifts observed in patients treated with alteplase plus thrombectomy. Thrombectomy alone did not show any safety advantages compared with alteplase plus thrombectomy. Furthermore, recanalisation rates and favourable clinical outcome in patients treated with intravenous alteplase plus thrombectomy were among the highest reported in comparable stroke trials and might serve as a benchmark for achievable results in the future.

Implications of all the available evidence

Our trial provides evidence that thrombectomy alone cannot be regarded as non-inferior to intravenous alteplase plus thrombectomy in patients from Europe and North America and decreased rates of reperfusion were observed among patients treated with thrombectomy alone. These results do not support omitting intravenous thrombolysis with alteplase before thrombectomy in eligible patients.

Introduction

In all the pivotal trials showing the benefit of thrombectomy for stroke, intravenous alteplase was given as concomitant treatment to all lytic-eligible patients.[1–8] It remains unknown whether thrombectomy alone is equally or more effective than intravenous alteplase plus thrombectomy if the endovascular intervention can be done immediately.[9–12] This trial was one of several contemporaneous randomised controlled trials comparing thrombectomy alone with intravenous alteplase plus thrombectomy.[13–17] Two trials from China (DIRECT-MT and DEVT)[14,15] found that, given the selected non-inferiority margins, thrombectomy alone was non-inferior to intravenous alteplase plus thrombectomy, whereas trials from Japan (SKIP)[16] and Europe (MR CLEAN-NO IV)[13] could not show non-inferiority. Between-study heterogeneity of patient population, stroke aetiology, and workflow organisation might explain these differences.[13–16] A study-level meta-analysis synthesising the primary outcome of the four trials concluded that thrombectomy alone is non-inferior to intravenous alteplase plus thrombectomy, considering most non-inferiority margins proposed in the literature.[18] However, non-inferiority according to the most conservative margin suggested by a stroke expert survey was not shown.[18,19] Consequently, there is clinical equipoise as to whether intravenous alteplase before thrombectomy can be omitted, and data from patients from Europe and North America are sparse. Therefore, further evidence from randomised controlled clinical trials that include European and Canadian patients and that have stringent inclusion and exclusion criteria is needed to further evaluate if thrombectomy alone is at least as effective and safe as intravenous alteplase plus thrombectomy. We did the SWIFT DIRECT trial to determine whether thrombectomy alone would be non-inferior to intravenous alteplase plus thrombectomy in directly admitted patients presenting with an acute ischaemic stroke.

Methods

Study design

In this investigator-initiated, multicentre, prospective, randomised, open-label, blinded-outcome trial, we

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compared thrombectomy alone with intravenous alteplase plus thrombectomy in patients presenting with an acute ischaemic stroke due to anterior circulation large vessel occlusion. The study enrolled patients eligible for both intravenous thrombolysis within 4·5 h after the time last seen well and endovascular thrombectomy. The study was done at 48 tertiary care centres in Europe and Canada. All centres had stroke units that offer thrombectomy 24 h a day.

Background and details of the trial design have been published previously.[20] The study was conducted and reported with fidelity to the study protocol (appendix pp 28–91). The protocol was approved by all relevant local ethics committees and research boards. There were four revisions of the protocol, one of which included changes to the inclusion and exclusion criteria (appendix pp 89–91).

Patients

Patients were eligible if they presented with occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both, confirmed with CT angiography or magnetic resonance (MR) angiography; were eligible to receive alteplase within 4 h and 30 min measured from the time when the patient was last seen well; could undergo thrombectomy within 75 min of randomisation; and had severe neurological deficits, defined as a National Institutes of Health Stroke Scale (NIHSS) score of 5 or more with an upper limit score of 30. There was no upper age limit; however, patients with advanced dementia or substantial pre-existing disabilities were excluded. To exclude participants with early signs of severe tissue loss, enrolment criteria required an Alberta Stroke Program Early CT Score (ASPECTS) of 4 or more on admission, non-contrast CT, or admission diffusion-weighted MRI. Patients presenting with a clinically significant ipsilateral atherosclerotic stenosis or occlusion of the cervical internal carotid artery were included. Detailed inclusion and exclusion criteria are provided in the appendix (pp 14–15). Enrolled patients or their next of kin provided written informed consent, or in selected countries a delayed informed consent was used in emergency circumstances.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to thrombectomy alone (intervention group) or intravenous alteplase plus thrombectomy (control group) using a centralised web server. A deterministic minimisation method was used for stratified randomisation taking into account the following dichotomised factors: NIHSS (≤17 *vs* >17), age (<70 years *vs* ≥70 years), occlusion location (M1 only versus intracranial internal carotid artery or intracranial internal carotid artery and M1), tandem lesion (tandem *vs* non-tandem), and ASPECTS (4–7 *vs* 8–10). Treatment group allocation was displayed to the treating physicians after randomisation. All personnel assessing the primary outcome were masked to group allocation, clinical information, and outcomes. The principal investigators and sponsors of the trial were fully masked to allocation, clinical data, and outcomes until the point of database lock after termination of the trial. The only information available was an allocation-blinded report of the interim analysis. The core laboratory staff were masked to group allocation, clinical information, and outcomes at all times.

Procedures

In both treatment groups, thrombectomy was initiated as fast as possible with any commercially available Solitaire stent-retriever revascularisation device (Medtronic, Irvine, CA, USA). Patients allocated to intravenous alteplase plus thrombectomy additionally received intravenous alteplase as early as possible after randomisation. Intravenous alteplase (0·9 mg/kg bodyweight with a maximum dose of 90 mg per patient) was administered for 60 min with 10% of the calculated dose given as an initial bolus. Unless there were medical contraindications (eg, ongoing bleeding), the complete dose of alteplase was administered. In both treatment groups, the use of a balloon guide catheter or distal aspiration catheter during thrombectomy was strongly encouraged, whereas intra-arterial administration of fibrinolytics was prohibited. Other concomitant treatments, medications, and postoperative care were guided by the international standard of care for intravenous thrombolysis and thrombectomy.[21–23] Follow-up clinical visits were scheduled for 24 h (± 6 h) for 7–10 days (or day of discharge), and 90 days (± 15 days) after the acute stroke event. At all visits, the neurological deficit, current medications, concomitant procedures, and adverse events were assessed. At visits seven to ten (or at discharge) and 90 days after randomisation, the degree of disability, resource utilisation, and quality of life were evaluated. The only scheduled imaging after treatment was planned at 24 h (± 6 h) after randomisation.

Outcomes

The primary binary outcome was a score of 2 or less on the modified Rankin scale at 90 days (functional independence). The modified Rankin scale is a 7-point scale of global disability ranging from 0 (no symptoms) to 6 (death). It was assessed by certified medical personnel masked to the treatment allocation, during a clinical visit or a structured telephone interview.

Secondary outcomes were mortality, ordinal degree of disability on the modified Rankin scale at 90 days (modified Rankin scale shift), change in the NIHSS score between admission and 24 h after randomisation, and quality of life as assessed by the EuroQol 5D-3L at 90 days.

The following secondary outcomes for technical efficacy of reperfusion were centrally assessed by an independent imaging core laboratory. Reperfusion occurring during the thrombectomy procedure itself was assessed by comparing initial and final digital subtraction angiography findings

and rated as: successful reperfusion, defined as expanded thrombolysis in cerebral infarction (TICI)[24] score 2b50–3, or complete reperfusion, defined as expanded TICI score 3; we also assessed time from admission to successful reperfusion. Additionally, reperfusion between initial CT or MR angiography and initial digital subtraction angiography, and reperfusion between initial CT or MR angiography and final digital subtraction angiography were rated with the cross-sectional expanded TICI (appendix p 6). This was a post-hoc analysis not prespecified in the protocol.

Prespecified safety outcomes were all serious adverse events, imaging core laboratory identified parenchymal haematoma type 1 or 2, subarachnoid haemorrhage or intraventricular haemorrhage at 24 h (± 6 h) after randomisation, symptomatic intracranial haemorrhage (SICH), and moderate or severe bleeding defined by Global Use of Strategies to Open Occluded Arteries at 24 h after randomisation. Two definitions of SICH were applied. The first was core-laboratory adjudicated parenchymal haematoma type 1 or 2, subarachnoid haemorrhage, or intraventricular haemorrhage within 24 h (± 6 h) associated with an increase of the NIHSS score of 4 or more compared with baseline ($SICH_{global}$). The second was site-investigator adjudicated evidence of any intracranial haemorrhage and site-investigator adjudicated neurological worsening of 4 points on the NIHSS compared with immediately before deterioration, most likely due to radiologically evident intracranial haemorrhage ($SICH_{site}$).

Statistical analysis

Sample size was based on the assumption that 62·2% of patients in the control group would be functionally independent at 90 days after randomisation and a non-inferiority margin of 12%. 404 participants were required for the study to achieve 80% power to detect non-inferiority at a one-sided significance level of 0·05. The estimated proportion of 62·2% was calculated using a weighted average of modified Rankin scale score of 0–2 in patients included in the best medical treatment plus thrombectomy treatment group of SWIFT PRIME and the expectation that 80% of patients would be directly admitted to a hospital capable of performing thrombectomy.[3] This reference was chosen because the SWIFT DIRECT inclusion criteria were very similar to SWIFT PRIME, and SWIFT DIRECT only included patients admitted directly to a thrombectomy centre (mothership model). Because centres enrolling patients in SWIFT DIRECT had a geographically different distribution, and organisation of stroke care differed from centres participating in SWIFT PRIME, for this outcome calculation we also included a weighted average of 20% SWIFT PRIME patients who were transferred from a centre without endovascular capability (drip and ship).

The initial considerations regarding the non-inferiority margin were based on a preserved fraction of at least 60% of the absolute clinical efficacy estimate of best medical treatment plus thrombectomy compared with best medical treatment observed in the SWIFT PRIME trial (35·5% had a modified Rankin scale score of 0–2 with best medical treatment *vs* 60·2% for thrombectomy; treatment effect 24·7%; 60% preservation=14·8%, non-inferiority margin 9·9%).[3] Owing to the wide variation of outcomes in the best medical treatment plus thrombectomy groups of SWIFT PRIME,[3] MR CLEAN,[1] and REVASCAT,[25] there was concern that the projected event rate in the control group of SWIFT DIRECT had poor precision. Another concern was that the constancy assumption might not hold in full, because technical advances (eg, higher rates of complete reperfusions) are likely to have increased the treatment effect of the active comparator over time. Therefore, the non-inferiority margin was widened to 12% in absolute terms, reflecting preservation of approximately 50% of the treatment effect of thrombectomy observed in SWIFT PRIME.[3]

Because overestimation of the active control event rate could underpower the trial, a prespecified sample size recalculation was done after 202 patients had reached the primary outcome. The re-estimation was based on the frequency of patients in the control group with a modified Rankin scale score of 0–2 at 90 days. The re-estimated sample size was lower than the initial one and no adjustment was made (as stipulated in the statistical analysis plan). There was no planned adjustment of the non-inferiority boundary during the trial.

The primary outcome was assessed for non-inferiority with the one-sided lower 95% confidence limit of the Mantel-Haenszel risk difference stratified according to randomisation strata. Non-inferiority would be claimed if it lay above –12% in both the intention-to-treat and per-protocol analyses. If non-inferiority was shown, a preplanned test for superiority of the experimental versus the control group at the nominal two-sided significance level of 0·05 using a stratified Cochran-Mantel-Haenszel test would be done. No type I error control was used for this test, as the multiple testing procedure is strictly hierarchical.

Secondary binary outcomes were analysed with the same method, but with a two-sided 95% CI. Continuous variables were analysed with linear regression with robust standard errors adjusted for randomisation strata and baseline values (for the NIHSS score). The modified Rankin scale was analysed using a proportional odds ordinal logistic regression with the treatment group and randomisation strata as covariates. Time to event data were analysed using flexible parametric survival models with the treatment group and randomisation strata as covariates. For mortality we report the risk difference at 90 days, and for the time to successful reperfusion, the mean restricted survival time truncated at the shorter of the maximum event times in the two groups.

The primary efficacy analyses were done according to the intention-to-treat principle including all randomly

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assigned and consenting patients (the full analysis set). Deceased patients were assigned a modified Rankin scale score of 6 and were excluded from the quality-of-life analysis. Missing outcome data were handled with multiple imputations (appendix pp 6–7) or censoring (for mortality). Multiple imputed datasets were used for all efficacy outcome analyses.

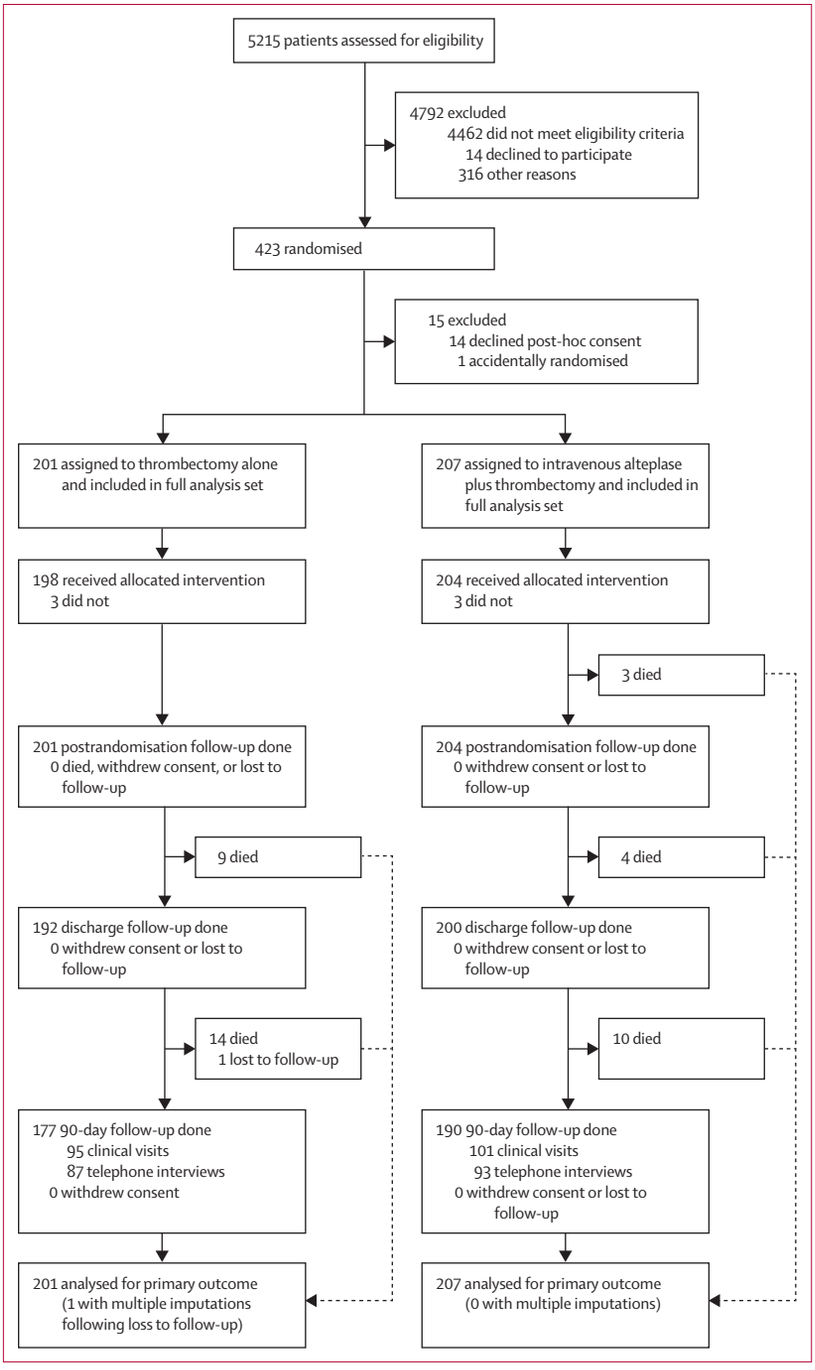

Figure 1: **Study flowchart**
Other reasons for exclusion were absence of the study team (n=237), inclusion in a competing trial (n=10), deemed not suitable for Solitaire stent retriever or thrombectomy by the local operator (n=23), out of working hours presentation (n=41), and an individual decision by the stroke consultant to prioritise thrombolysis with alteplase (n=5). At 90-day follow-up, some patients had both a clinical visit and a telephone interview, which is why these two categories add up to more than the total marked as followed up.

The primary outcome was analysed for predefined subgroups (randomisation strata, protocol version) and a post-hoc subgroup (sex) using logistic regression models with the treatment group, the subgroup, and their interaction as covariates (appendix p 8).

The safety population consisted of all participants in the full analysis set who received one of the study interventions, including patients who did not undergo thrombectomy owing to preinterventional reperfusion. Participants were analysed according to the treatment they actually received (as treated).

All analyses were done by a trial statistician using STATA version 17.0, and plots were drawn in R version 4.0.3. A second statistician reproduced the main, per-protocol, and complete case analysis of the primary outcome using R version 3.6.0 (appendix p 9).

This trial is registered with ClinicalTrials.gov (NCT03192332) and is closed to new participants.

Role of the funding source

The study was supported by a research grant from Medtronic to the University Hospital Bern. The funder (Medtronic) was not involved in data collation, analysis, interpretation, writing of the manuscript, or the decision to submit.

Results

Between Nov 29, 2017, and May 7, 2021, 423 patients at 42 centres were randomly assigned (appendix pp 10, 16). 15 patients were excluded after randomisation (14 declined post-hoc consent and one owing to an accidental web-browser randomisation during the eligibility check). For each patient excluded, a new patient was randomly assigned. The trial enrolled to completion with a total of 201 patients assigned to receive thrombectomy alone and 207 patients assigned to receive intravenous alteplase plus thrombectomy (figure 1). 402 received the allocated intervention. There were three crossovers in each treatment group and other major prespecified protocol violations were documented in 64 patients (appendix p 17). The primary outcome data were multiply imputed for one patient lost to follow-up and assigned to thrombectomy alone. The characteristics of the patients at baseline are in table 1 and the appendix (p 18).

The median delay from arrival at the emergency department to administration of intravenous alteplase was 55 min (IQR 38–71) and the full dose was administered to 198 (96%) of 207 patients assigned to receive intravenous alteplase (appendix p 19). Catheter angiography was done in all patients. All patients assigned to thrombectomy alone underwent thrombectomy, whereas seven patients assigned to intravenous alteplase plus thrombectomy did not undergo thrombectomy (due to partial or complete

	Thrombectomy alone (n=201)	Intravenous alteplase plus thrombectomy (n=207)
Age, years	73 (64 to 81)	72 (65 to 81)
Sex		
Male	96 (48%)	103 (50%)
Female	105 (52%)	104 (50%)
NIHSS score*	17 (13 to 20)	17 (12 to 20)
Prestroke score on the modified Rankin scale†		
0	167 (83%)	179 (86%)
1	34 (17%)	27 (13%)
4	0 (0%)	1 (0%)
Systolic blood pressure, mm Hg‡	147 (130 to 160)	148 (134 to 165)
Blood glucose level, mmol/L§	6·5 (5·8 to 7·5)	6·6 (5·8 to 7·6)
Risk factors¶		
Previous ischaemic stroke		
No	172 (86%)	181 (87%)
Yes	21 (10%)	20 (10%)
Unknown	8 (4%)	6 (3%)
Previous transient ischaemic attack		
No	182 (91%)	186 (90%)
Yes	7 (3%)	14 (7%)
Unknown	12 (6%)	7 (3%)
History of hypertension		
No	75 (37%)	84 (41%)
Yes	121 (60%)	118 (57%)
Unknown	5 (2%)	5 (2%)
History of atrial fibrillation		
No	172 (86%)	176 (85%)
Yes	17 (8%)	22 (11%)
Unknown	12 (6%)	9 (4%)
History of hypercholesterolaemia		
No	133 (66%)	123 (59%)
Yes	60 (30%)	71 (34%)
Unknown	8 (4%)	13 (6%)
Baseline imaging‖		
CT	105 (52%)	100 (48%)
MRI	95 (47%)	105 (51%)
Both	1 (0%)	2 (1%)
ASPECTS**	8 (7 to 9)	8 (7 to 9)
Baseline intracranial occlusion site††		
ICA	57 (28%)	60 (29%)
M1	133 (66%)	136 (66%)
M2	11 (5%)	11 (5%)
Tandem lesion‡‡	30 (15%)	33 (16%)
Duration, min		
Stroke onset to randomisation§§	123 (99 to 163)	135 (106 to 171)
Time from arrival at emergency department to intravenous alteplase ¶¶	55 (38 to 79)	55 (38 to 71)
Time from arrival at emergency department to groin arterial puncture	75 (60 to 90)	80 (63 to 101)
Start of intravenous alteplase to arterial puncture¶¶	3·0 (–56 to 40)	24 (15 to 35)

Data are median (IQR) or n (%). NIHSS=National Institutes of Health Stroke Scale. ASPECTS=Alberta Stroke Program Early CT Score. ICA=internal carotid artery. M1=first segment of the middle cerebral artery. M2=second segment of the middle cerebral artery. MR=magnetic resonance. *Scores on the NIHSS range from 0 to 42, with 0 indicating no deficits and a higher score indicating more severe neurological symptoms. †Scores on the modified Rankin scale range from 0 (no symptoms) to 6 (death). Prestroke disability was assessed by the treating physician with information provided by the patient, health-care records, or family members. ‡Data were missing for one patient in the thrombectomy alone group and four patients in the intravenous alteplase plus thrombectomy group. §Data were missing for 12 patients in the thrombectomy alone group and 11 patients in the intravenous alteplase plus thrombectomy group. ¶Risk factors denote known risk factors according to the medical history of the patient. This excludes de-novo detection of atrial fibrillation or arterial hypertension during the acute hospital stay. ||Baseline imaging modality was chosen according to the standard of care of the enrolling centre. **ASPECTS evaluates early ischaemic changes in the hypoperfused territory. A score of 10 indicates absence of such changes, and one point is subtracted for each standardised brain region in the middle cerebral artery territory that exhibits such changes. ASPECTS was evaluated on non-contrast CT images or diffusion-weighted imaging if patients underwent MRI. For diffusion-weighted imaging-based ASPECTS evaluation, a region has to have a diffusion abnormality in 20% or more of its volume to be considered positive for early ischaemic changes. ASPECTS was missing for one patient in the intravenous alteplase plus thrombectomy group. ††Baseline intracranial occlusion site was adjudicated by the imaging core laboratory. In three patients in the thrombectomy alone group and six patients in the intravenous alteplase plus thrombectomy group, baseline occlusion location was rated on first invasive angiography images, because baseline imaging did not include CT or MR angiography, or it was of poor quality and occlusion location could not be deduced from other available sequences of the baseline imaging. In one patient in the thrombectomy alone group and two patients in the intravenous alteplase plus thrombectomy group, baseline occlusion location was rated on baseline imaging using a synopsis of available sequences, but CT or MR angiography was not available or was of poor quality. In all other patients, baseline occlusion location was rated on CT or MR angiography images. ‡‡Tandem lesion was defined as clinically significant atherosclerotic stenosis or complete atherosclerotic occlusion of the extracranial internal carotid artery ipsilateral to the intracranial target occlusion. Tandem lesion was a stratification factor and was site-adjudicated at the time of randomisation. §§Data were missing for one patient in the thrombectomy alone group and these data were imputed from time of arrival and thrombectomy device deployment. ¶¶Data were available for three patients in the thrombectomy alone group (crossover) and missing for three patients in the intravenous alteplase plus thrombectomy group (crossover). In one of the three patients assigned to the thrombectomy alone group, who received intravenous alteplase, it was administered after arterial puncture.

Table 1: **Patients' baseline characteristics**

reperfusion [n=5], failed intracranial access due to tortuous cervical vessels [n=1], and after thrombus migration following carotid puncture [n=1]). Details of the thrombectomy procedure are provided in the appendix (p 20).

The primary outcome of modified Rankin scale score of 0–2 at 90 days was reached by 114 (57%) of 201 patients assigned to thrombectomy alone and 135 (65%) of 207 patients assigned to intravenous alteplase plus thrombectomy (adjusted risk difference –7·3%, 95% CI –16·6 to 2·1, lower limit of one-sided 95% CI –15·1%, crossing the predefined non-inferiority margin of –12%;

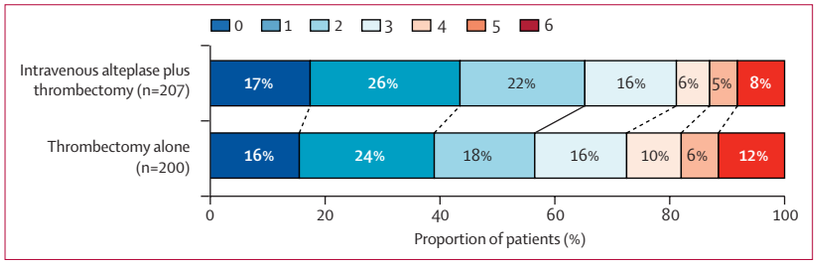

Figure 2: **Modified Rankin scale scores at 90 days**
Modified Rankin scale scores are shown for patients for whom data were available. Scores range from 0 (no symptoms) to 6 (death). The solid line between the stacked bar charts shows the cutoff for functional independence (modified Rankin scale 0–2). This was reached in 113 (57%) of 200 (114 of 201 based on multiple imputations) patients assigned to thrombectomy alone and 135 (65%) of 207 assigned to thrombectomy combined with intravenous thrombolysis (adjusted risk difference with one missing outcome in the thrombectomy alone group imputed: −7·3%, 95% CI −16·6 to 2·1). The predefined non-inferiority margin of 12% was not met (lower limit of the one-sided 95% CI −15·1%). Percentages do not add up to 100% due to rounding.

figure 2, table 2). The non-inferiority margin of −12% was also crossed when restricting analyses to other predefined populations (appendix pp 21–23). Because of failure to show non-inferiority of thrombectomy alone, all subsequent analyses were exploratory without formal type-I error control.

Prespecified secondary clinical efficacy outcomes and technical efficacy outcomes are shown in table 2. At 90 days, 22 (11%) of 201 patients assigned to thrombectomy alone and 17 (9%) of 207 patients assigned to intravenous alteplase plus thrombectomy had died (risk difference 2·3%, 95% CI −3·2 to 7·8, appendix p 11). There were no significant differences regarding the full distribution of modified Rankin scale scores at 90 days (common odds ratio for a better outcome 0·75, 95% CI 0·53–1·06, p=0·10).

Successful reperfusion before thrombectomy (cross-sectional expanded TICI 2b50–3) occurred in two (1%) of 201 patients assigned to thrombectomy alone and eight (4%) of 207 patients assigned to intravenous alteplase plus thrombectomy (risk difference −2·9%, 95% CI −6·0 to 0·3%, p=0·077). After completion of all endovascular procedures, successful reperfusion was less frequently observed in patients assigned to thrombectomy alone (cross-sectional expanded TICI 2b50–3 in 182 (91%) of 201 *vs* 199 (96%) of 207, risk difference −5·1%, 95% CI −10·2 to 0·0%, p=0·047). In the complete cohort, only two (7%) of 27 patients in whom reperfusion was not successful (cross-sectional expanded TICI <2b50) were functionally independent at 90 days.

Central adjudicated symptomatic intracranial haemorrhage ($SICH_{global}$) occurred in five (2%) of 201 patients undergoing thrombectomy alone and seven (3%) of 202 patients receiving intravenous alteplase plus thrombectomy (risk difference −1·0%, 95% CI −4·8 to 2·7, table 3). The occurrence of serious adverse events did not differ between patients receiving thrombectomy alone (56 [28%] of 201) and those treated with intravenous alteplase plus thrombectomy (54 [26%] of 207; risk difference 1·8%, 95% CI −6·8 to 10·3). A list of serious adverse events in both treatment groups with additional strata of causality, intensity, and outcome can be found in the appendix (pp 24–25), and interventional complications and prespecified adverse events at day 1 are listed in the appendix (p 26). In five (2%) of 207 patients receiving intravenous alteplase, a serious adverse event was rated as probably or highly probably related to administration of intravenous alteplase, whereas no serious adverse events were rated as probably or highly probably related to the omission of intravenous alteplase.

With the exception of age, no evidence was found of treatment effect modification (appendix pp 12–13). The primary outcome was observed comparably often in both treatment groups when considering patients aged 70 years or older (risk difference −2·2%, 95% CI −14·4 to 10·1, lower limit of one-sided 95% CI −12·4%, just crossing the non-inferiority margin of 12%). In patients younger than 70 years, however, the primary outcome was significantly less often observed in the thrombectomy alone group (risk difference −18·9%, 95% CI −32·2 to −5·7, p=0·0051, $p_{interaction}$=0·039). The non-inferiority margin of 12% was crossed in all subgroups analysed.

Discussion

This study compared thrombectomy alone to intravenous alteplase plus thrombectomy in lytic-eligible patients with acute ischaemic stroke due to large vessel occlusion in the anterior circulation who arrived directly at stroke centres, where fast access to endovascular stroke treatment can be guaranteed. Despite strict inclusion and exclusion criteria aimed at studying a population of true clinical equipoise, non-inferiority of thrombectomy alone compared with intravenous alteplase plus thrombectomy in yielding functional independence at 3 months could not be shown. Notably, point estimates directionally favoured intravenous alteplase plus thrombectomy and similar outcome patterns were seen for all secondary clinical efficacy measures. Although alteplase-associated preinterventional reperfusion occurred infrequently, final postinterventional reperfusion rates were higher in patients assigned to intravenous alteplase plus thrombectomy, a significant difference not previously reported.[13–16]

Rates of good functional outcome in SWIFT DIRECT were higher than in previous trials comparing thrombectomy alone versus thrombectomy with intravenous alteplase.[13–16] The overall high rates of good outcome and successful reperfusion in this trial might reflect conservative selection of ideal candidates for thrombectomy, frequent use of flow-arrest devices, and the overall high standard of care of participating centres. In contrast to some of the other trials comparing thrombectomy alone versus intravenous alteplase plus thrombectomy,[13–16] the present trial specifically excluded patients presenting with M2 occlusions, cervical vessel

	Thrombectomy alone (n=201)		Intravenous alteplase plus thrombectomy (n=207)		Measure of effect	Adjusted effect (95% CI)†	p value‡
	N* (imputed)	n (%) or median (IQR)	N* (imputed)	n (%) or median (IQR)			
Primary outcome							
Modified Rankin scale score 0–2	201 (1)	114 (57%)	207 (0)	135 (65%)	Risk difference	−7·3% (−16·6 to 2·1); lower limit of one-sided 95% CI −15·1%§	..
Secondary clinical efficacy outcomes							
Mortality at 90 days¶	201	22 (11%)	207	17 (9%)	Risk difference	2·3% (−3·2 to 7·8)	0·41
Modified Rankin scale score	201 (1)	2 (1 to 4)	207 (0)	2 (1 to 3)	Common odds ratio (for a better outcome)	0·75 (0·53 to 1·06)	0·10
Change in NIHSS between admission and 24 h	201 (4)	−9·0 (−14 to −1·7)	207 (7)	−10 (−14 to −4·0)	Mean difference	0·92 (−0·59 to 2·42)	0·23
Quality-of-life dimensions‖							
Any problems with mobility	178 (10)	84 (47%)	190 (7)	71 (37%)	Risk difference	7·9% (−2·5 to 18·1)	0·14
Any problems with self-care	178 (11)	57 (32%)	190 (8)	55 (29%)	Risk difference	0·5% (−9·0 to 10·0)	0·91
Any problems with usual activities	178 (11)	96 (54%)	190 (7)	97 (51%)	Risk difference	2·1% (−8·3 to 12·4)	0·70
Any problems with pain or discomfort	178 (10)	96 (54%)	190 (9)	84 (44%)	Risk difference	9·6% (−1·2 to 20·2)	0·082
Any problems with anxiety or depression	178 (13)	75 (42%)	190 (10)	84 (44%)	Risk difference	−3·1% (−13·9 to 7·8)	0·58
Visual analogue scale	178 (29)	70 (50 to 80)	190 (29)	70 (60 to 85)	Mean difference	−4·78 (−10·0 to 0·42)	0·072
Secondary technical efficacy outcomes							
Mean time from emergency department arrival to successful reperfusion (95% CI), min	201 (21)	125 (119 to 131)	207 (12)	123 (118 to 128)	Restricted mean survival time difference	2·2 (−5·8 to 10)	0·59
Preinterventional expanded TICI 2b50–3**	201 (2)	1 (<1%)	207 (1)	2 (1%)	Risk difference	−0·3% (−2·0 to 1·4)	0·71
Final expanded TICI 2b50–3**	201 (3)	182 (91%)	207 (8)	199 (96%)	Risk difference	−5·1% (−10·2 to 0)	0·047
Final expanded TICI 3**	201 (3)	67 (33%)	207 (8)	75 (36%)	Risk difference	−3·9% (−13·4 to 5·6)	0·41
Preinterventional cross-sectional expanded TICI 2b50–3††	201 (5)	2 (1%)	207 (7)	8 (4%)	Risk difference	−2·9% (−6·0 to 0·3)	0·077
Final cross-sectional expanded TICI 2b50–3††	201 (5)	182 (91%)	207 (7)	199 (96%)	Risk difference	−5·1% (−10·2 to 0·0)	0·047

Data are N* (imputed n), n (%), or median (IQR), unless otherwise specified. NIHSS=National Institutes of Health Stroke Scale. TICI=thrombolysis in cerebral infarction. *Number of non-missing data. †The analyses were stratified or adjusted with randomisation strata. Crude results, a complete case analysis, and analysis of a per-protocol population are presented in the appendix (pp 21–23). ‡No adjustment for multiple testing has been made for any of the secondary outcomes. §Lower than the non-inferiority margin of −12%; thus, non-inferiority cannot be claimed. ¶As per the statistical analysis plan, mortality was defined as all-cause mortality at 90 days. One patient assigned to thrombectomy alone died after 99 days, before the day 90 assessment was done. For the modified Rankin scale score distribution of the day 90 assessment, this patient was assigned a score of 6, while he was rated as alive for all-cause mortality at 90 days. ‖Excluding 40 patients who were not alive at the day 90 assessment. **Grades on the expanded TICI range from 0 (no reperfusion) to 3 (complete reperfusion), with grades higher than or equal to 2b50 defined as successful reperfusion. Preinterventional and postinterventional expanded TICI was assessed by the imaging core laboratory on preinterventional or postinterventional digital subtraction catheter angiography images. ††Cross-sectional expanded TICI refers to reperfusion grading relative to the occlusion site on baseline cross-sectional imaging. Preinterventional and postinterventional cross-sectional expanded TICI was assessed by the imaging core laboratory on preinterventional or postinterventional digital subtraction catheter angiography images and with reference to the baseline cross-sectional imaging.

Table 2: **Primary and secondary efficacy outcomes**

tortuosity, and multi-vessel occlusions. Despite this strict candidate selection aimed at studying a population with the best chances of good reperfusion following endovascular treatment, a 5% absolute reduction in the rates of successful reperfusion was found in patients assigned to thrombectomy alone compared with those who received alteplase plus thrombectomy. No other trial comparing direct thrombectomy to intravenous alteplase plus thrombectomy found a significant difference in the rate of successful reperfusion after endovascular treat_ment, although all trials reported numerical differences in the same direction (ie, favouring the intravenous

	Received thrombectomy alone (n=201), n/N* (%)	Received intravenous alteplase plus thrombectomy (n=207), n/N* (%)	Risk difference (95% CI)	p value
Any intracranial haemorrhage up to 24 h†	59/201 (29%)	69/205 (34%)	−4·3% (−13·2 to 4·7)	0·39
Radiological bleeding classification†‡				
Subarachnoid haemorrhage	16/201 (8%)	18/205 (9%)	−0·8% (−6·4 to 4·7)	0·86
Parenchymal haemorrhage type 1	1/201 (<1%)	0/205	0·5% (−1·4 to 2·8)	0·50
Parenchymal haemorrhage type 2	2/201 (1%)	6/205 (3%)	−1·9% (−5·3 to 1·1)	0·28
Haemorrhagic infarction type 1	28/201 (14%)	33/205 (16%)	−2·2% (−9·2 to 4·8)	0·58
Haemorrhagic infarction type 2	14/201 (7%)	15/205 (7%)	−0·4% (−5·6 to 4·9)	1·00
$SICH_{global}$§	5/201 (2%)	7/202 (3%)	−1·0% (−4·8 to 2·7)	0·77
$SICH_{site}$¶	3/201 (1%)	10/204 (5%)	−3·4% (−7·4 to 0·2)	0·087
Severe and moderate systemic bleeding up to 24 h	1/201 (<1%)	4/204 (2%)	−1·5% (−4·5 to 1·1)	0·37
Groin haematoma (up to discharge or 7–10 days ‖)	4/201 (2%)	12/207 (6%)	−3·8% (−8·0 to 0·1)	0·072
Femoral artery pseudoaneurysm (up to discharge or 7–10 days ‖)	1/201 (<1%)	5/207 (2%)	−1·9% (−5·1 to 0·7)	0·22
Any serious adverse event (within 90 days)**	56/201 (28%)	54/207 (26%)	1·8% (−6·8 to 10·3)	0·74

Data are n/N* (%), unless otherwise specified. SICH=symptomatic intracranial haemorrhage. NIHSS=National Institutes of Health Stroke Scale. *Number of patients with non-missing data. †Adjudicated by the imaging core laboratory. ‡Numbers do not add up as four patients had both subarachnoid haemorrhage and haemorrhagic infarction type 2 and one patient had subarachnoid haemorrhage and parenchymal haemorrhage type 2. §$SICH_{global}$ was adjudicated by the imaging core laboratory and was defined as the occurrence of parenchymal haemorrhage type 1, parenchymal haemorrhage type 2, subarachnoid haemorrhage or intraventricular haemorrhage, and an increase of NIHSS of more than 4 points between admission and 24 h after randomisation. ¶$SICH_{site}$ was adjudicated by the local investigators if there was radiological evidence of intracranial haemorrhage and the patient had an increase of 4 or more points on the NIHSS compared with immediately before deterioration. The imaging core laboratory assigned the following radiological bleeding class to 13 patients: subarachnoid haemorrhage (n=4), subarachnoid haemorrhage and haemorrhagic infarction type 2 (n=1), parenchymal haemorrhage type 2 (n=4), and haemorrhagic infarction type 2 (n=3); for one patient, follow-up imaging was unavailable to the imaging core laboratory. ‖Or up to the time of death for the 16 patients that died earlier. **One patient who underwent thrombectomy alone without serious adverse event and was lost to follow-up after 9 days is included here.

Table 3: **Trial safety outcomes**

alteplase plus thrombectomy group).[13–16] The magnitude of this effect appears to be clinically relevant as successful reperfusion is one of the most important determinants of clinical outcome and an absolute increase of 5% in successful reperfusion is considered meaningful to patients.[26] One potential reason why such a difference was not reported by other trials might be that the current study included only a minority of patients treated with aspiration, which has been associated with lower rates of successful reperfusion when combined with intravenous alteplase.[27] Hence, a potential negative effect of treatment with intravenous alteplase plus aspiration might have been averted, and use of stent retrievers with concomitant proximal flow-arrest or distal aspiration seemed to translate into an overall favourable reperfusion rate in patients treated with intravenous alteplase plus thrombectomy. The difference in reperfusion rates seems to be mainly driven by more successful interventions because differences due to preinterventional reperfusion are neglected by the classic TICI grading.[28] The rate of successful preinterventional reperfusion did not differ significantly between the two treatment groups, although it was numerically higher in patients assigned to intravenous alteplase plus thrombectomy.

As fewer than 10% of patients without successful reperfusion reached functional independence in this trial, the difference in reperfusion rates might have translated into numerical differences in functional outcomes, favouring the intravenous alteplase plus thrombectomy group. Consequently, the liberal margin of 12% based upon the hypothesis of a reasonable clinical comparability was not met.[20] This result aligns with the results of the MR CLEAN-NO IV and SKIP trials,[13,16] but contrasts with the results of two trials enrolling patients in China (DIRECT-MT and DEVT).[14,15] These trials, which also used broad non-inferiority margins, found thrombectomy alone to be non-inferior to intravenous alteplase plus thrombectomy.[14,15] Interestingly, the workflow metrics and interventional characteristics of patients treated in the DEVT and DIRECT-MT trials were very similar to SWIFT DIRECT, highlighting that these factors alone are unlikely to explain the effect size differences observed among the trials. Although it is still possible that a combination of varying reperfusion rates and differences in inclusion and exclusion criteria might be the cause of the inter-trial differences observed, the exact interplay and potential causal relationships need to be determined.

Given the results reported here and the fact that the only other trial evaluating thrombectomy alone in White patients also did not show non-inferiority,[13] omitting intravenous alteplase in this population seems unjustified.

Administration of intravenous alteplase did not increase the risk of symptomatic intracranial haemorrhage, although the statistical power to detect a difference was limited by the small number of symptomatic bleeds. An individual patient data meta-analysis of trials comparing intravenous alteplase with placebo or open control found that intravenous alteplase led to a 5·5% absolute increase in the risk of type 2 parenchymal haemorrhage (6·8% *vs* 1·3%).[29] Besides power considerations related to study size, the lack of a clear association of intravenous alteplase with increased bleeding risk in this study might also be associated with overall good reperfusion, which seems to protect patients from haemorrhages and haemorrhagic transformations.[30,31]

Hypothesis-generating subgroup analyses suggested heterogeneity of the comparison of thrombectomy alone versus intravenous alteplase plus thrombectomy with regard to age. In contrast to the overall study results, the treatment effect was close to the null effect in patients aged 70 years or older, but still crossed the non-inferiority margin of 12%. A differential effect of alteplase according to age was not anticipated, as trials comparing

intravenous alteplase with placebo did not detect an age-related change in the effect of alteplase on the odds of good outcome.[32] In addition, no other trial found comparable heterogeneity of the relative treatment effect with age strata.[13–16] Until further evidence becomes available, this observation should be treated with caution, because there is a non-negligible likelihood that the observed heterogeneity is due to chance.

Our study has some limitations. First, most patients were treated with a specific type of stent retriever, so the results are not transferable to other stent retrievers or other thrombectomy devices. Second, although time from admission to administration of intravenous alteplase was longer than in the MR CLEAN-NO IV trial, this did not result in a poorer overall outcome.[13] Furthermore, speed of alteplase initiation was faster than in large registries, suggesting generalisability to current clinical practice.[33] However, there remains a possibility that owing to changes in imaging acquisition workflow (cervical vessel anatomy needed to be assessed before inclusion in the trial), some additional delay could have occurred in centres that usually administer intravenous alteplase before CT or MR angiography is done. To mitigate the chances of delays, an extensive and detailed feasibility check of the participating centres was done to ensure that all of them could provide fast CT angiography acquisition directly after non-contrast CT or MR angiography acquisition after fluid-attenuated inversion recovery, diffusion-weighted, or T2* imaging. Moreover, all centres had to provide staff for parallel consenting and randomisation so that clinical decisions by the treating physicians and image acquisitions were not delayed. During each trial initiation visit, the importance of this issue was highlighted, and a discussion was held with each centre about how the delay associated with the requirement for a CT or MR angiography before inclusion could be minimised. This included immediate acquisition of CT angiography and changes to MRI protocols to keep delays to a minimum. Third, the study was powered to assess a broad non-inferiority margin. Analyses of pooled data of individual participants from multiple trials are desirable to improve precision of the findings. Fourth, per-protocol analysis was limited to 339 (83%) of 408 patients, with the main protocol violation being evaluation of the primary endpoint outside the defined assessment period. Fifth, the population in our trial was confined to patients directly admitted to comprehensive stroke centres where fast access to endovascular stroke treatment can be guaranteed and results are not transferable to other clinical workflows. Sixth, approximately half of the patients were randomly assigned after undergoing admission MRI, which might further limit the generalisability of the data.

In conclusion, non-inferiority of thrombectomy alone when compared with intravenous alteplase plus thrombectomy in patients presenting with acute ischaemic stroke due to large vessel occlusion in the anterior circulation could not be shown, and omitting intravenous alteplase before thrombectomy was associated with decreased rates of successful reperfusion. In light of conflicting previous trial results and the evidence reported here of reduced reperfusion rates in patients treated with thrombectomy alone, omitting intravenous alteplase before thrombectomy in eligible patients cannot be recommended.

Contributors

JG and UF provided the overall principal leadership for the study. The Article was written by JK, UF, JLS, and JG. Statistical analyses and drawing of figures were done in STATA by LHB. All authors contributed to data acquisition and made critical revisions to the manuscript. LHB, PP, and SD had full access to the data or verified the underlying raw data. UF, JK, LHB, JLS, and JG were responsible for the decision to submit the manuscript. The design, analysis, and data collection for this trial were done by a steering committee consisting of academic investigators. The site investigators gathered the data, whereas monitoring and database maintenance were done by the sponsor and respective third party. The academic authors had unrestricted access to the data and the data analysis was done by an independent study statistician who attests the integrity of the analyses and the completeness and accuracy of the reported data. The steering board and all investigators vouch for the accuracy and completeness of the data, for the fidelity of the trial to the protocol, and for the complete reporting of any adverse events.

Declaration of interests

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Data sharing

Data from the SWIFT DIRECT trial are not publicly available but are planned to be made available in the future. A complete deidentified dataset will be made accessible, together with a data dictionary. Requests for access to the data can be made by sending an email together with a research plan to urs.fischer@usb.ch.

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