Thrombectomy Alone Versus Intravenous Alteplase Plus Thrombectomy in Patients with Stroke: A Randomized Controlled Non-Inferiority Trial

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ABSTRACT

BACKGROUND

Whether thrombectomy alone is equally as effective as intravenous alteplase (IVT) plus thrombectomy remains controversial.

METHODS

In this multicenter, randomized, open-label, blinded-outcome trial in Europe and Canada, stroke patients with large vessel occlusion admitted to endovascular centers were randomly assigned (1:1 ratio) to receive stent-retriever thrombectomy alone or IVT plus stent-retriever thrombectomy. The primary binary outcome was a score of ≤2 on the modified Rankin scale (mRS) at 90 days. We assessed the non-inferiority of thrombectomy alone versus IVT plus thrombectomy in the intention-to-treat population 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 hemorrhage. This trial is registered with ClinicalTrials.gov, NCT03192332.

FINDINGS

Of the 408 patients randomized, an mRS score of 0–2 at 90 days was reached by 114 (57%) assigned to thrombectomy alone and 135 (65%) assigned to IVT 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 hemorrhage occurred in five patients undergoing thrombectomy alone and seven patients receiving IVT plus thrombectomy (risk difference −1·0%, 95% CI −4·8 to 2·7%). Successful reperfusion was less common in patients assigned to thrombectomy alone (n=182, 91% versus n=199, 96%, 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 IVT plus thrombectomy and resulted in decreased reperfusion rates. These results do not support omitting IVT before MT in eligible patients.

FUNDING

Medtronic and University Hospital Bern.

Research in context

Evidence before this study

Whether thrombectomy alone is equally as effective as intravenous alteplase plus thrombectomy in acute stroke patients with large vessel occlusions admitted to centers with endovascular facilities remains controversial. We searched PubMed for randomized controlled trials published in English up to 2 January 2022, which compared thrombectomy alone with intravenous alteplase plus thrombectomy in acute stroke patients. 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 randomized controlled trials met the criteria. Two trials from China (DIRECT-MT, 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 demonstrate non-inferiority. There was considerable between-study heterogeneity regarding patient population, stroke etiology, and workflow organization, which may explain why some trials formally demonstrated non-inferiority, while 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 Caucasian patients.

Added value of this study

The SWIFT DIRECT trial could not demonstrate 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 favored intravenous thrombolysis plus thrombectomy. Although alteplase-associated pre-interventional reperfusion occurred infrequently, final post-interventional reperfusion rates were higher in patients assigned to intravenous alteplase plus thrombectomy, a significant difference not reported previously and a likely reason for the favorable outcome shifts observed in patients treated with alteplase plus thrombectomy. Thrombectomy alone did not show any safety advantages compared with alteplase plus thrombectomy. Furthermore, recanalization rates and favorable clinical outcome in patients treated with intravenous thrombolysis plus thrombectomy were among the highest reported in comparable stroke trials and may 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 Caucasian patients 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 demonstrating 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 performed immediately.[9–12]

This trial was one of several contemporaneous randomized controlled trials comparing thrombectomy alone with intravenous alteplase plus thrombectomy.[13–16] Two trials from China (DIRECT-MT [Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: a Multicenter Randomized Clinical Trial] and DEVT [Direct Endovascular Thrombectomy versus Combined IVT and Endovascular Thrombectomy for Patients with Acute Large Vessel Occlusion in the Anterior Circulation]) found that, given the selected non-inferiority margins, thrombectomy alone was non-inferior to intravenous alteplase plus thrombectomy, [14,15] whereas trials from Japan (SKIP [Direct Mechanical Thrombectomy in Acute LVO Stroke])[16] and Europe (MR CLEAN [Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands]–NO IV)[13] could not demonstrate non-inferiority. Between-study heterogeneity of patient population, stroke etiology, and workflow organization may explain these differences.[13–16] A study-level meta-analysis synthesizing 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.[17] However, non-inferiority according to the most conservative margin suggested by a recent stroke expert survey was not demonstrated.[17,18]

Consequently, there is clinical equipoise as to whether intravenous alteplase before thrombectomy can be omitted, and data from Caucasian populations are sparse. Therefore, further evidence from randomized controlled clinical trials that include European and Canadian patients and 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 conducted the Solitaire With the Intention For Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke (SWIFT DIRECT) trial to determine whether thrombectomy alone would be non-inferior to intravenous alteplase plus thrombectomy in directly admitted patients presenting with an acute ischemic stroke.

Methods

Trial Design and Oversight

In this investigator-initiated, multicenter, prospective, randomized, open-label, blinded-outcome trial, we compared thrombectomy alone with intravenous alteplase plus thrombectomy in patients presenting with an acute ischemic stroke due to anterior circulation large vessel occlusion. The study enrolled patients eligible for both intravenous thrombolysis within 4.5 hours after the time last seen well and endovascular thrombectomy.

Patients were randomly allocated to one of two treatment groups: Thrombectomy alone with any of the commercially available Solitaire™ stent-retrievers (intervention group) or intravenous alteplase plus thrombectomy with any of the commercially available Solitaire™ stent-retrievers (control group). Background and details of the trial design

have been published previously.[19] The study was conducted and reported with fidelity to the study protocol, available with the full text of this article.

Enrolled patients or their next of kin provided written informed consent, or in selected countries, a delayed informed consent was used in emergency circumstances. 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 (see Trial Protocol).

The design, analysis, and data collection for this trial were performed by a steering committee consisting of academic investigators. The site investigators gathered the data, whereas monitoring and database maintenance were performed by the sponsor and respective third party. The academic authors had unrestricted access to the data and the data analysis was performed 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.

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

Patients and Participating Centers

The study was conducted at 48 centers in Europe and Canada. All were tertiary care centers with stroke units that offer thrombectomy 24 hours a day. Patients were eligible if they presented with a computed tomography angiography (CTA)- or magnetic resonance angiography (MRA)-confirmed occlusion of the intracranial internal carotid

artery, the first segment of the middle cerebral artery, or both; were eligible to receive alteplase within 4 hours and 30 minutes measured from the time when the patient was last seen well; could undergo thrombectomy within 75 minutes of randomization; and had severe neurological deficits, defined as a National Institutes of Health Stroke Scale (NIHSS) score of ≥5 with an upper limit score of 30. There was no upper age limit; however, patients with advanced dementia or significant preexisting disabilities were excluded. To exclude subjects with early signs of a severe tissue loss, enrolment criteria required an Alberta Stroke Program Early CT Score (ASPECTS) of ≥4 on admission, non-contrast CT, or admission MRI diffusion-weighted imaging. 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 Table S1 in the Supplemental Appendix.

Randomization and Masking

Patients were randomly assigned in a 1:1 ratio using a centralized web server. A probabilistic minimization method was used for stratified randomization taking into account the following dichotomized factors: NIHSS (≤17 versus >17), age (<70 years versus ≥70 years), occlusion location ("M1 only" versus "intracranial ICA or intracranial ICA and M1"), tandem lesion (tandem versus non-tandem) and ASPECTS (4–7 versus 8–10). Treatment group allocation was displayed to the treating physicians after randomization. All personnel assessing the primary outcome were blinded to group allocation, clinical information and outcomes. The principal investigators and sponsors of the trial were fully blinded 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 lab was blinded to group allocation, clinical information and outcomes at all times.

Treatment

In both treatment groups, thrombectomy was initiated as fast as possible using any commercially available Solitaire stent-retriever revascularization device. Patients allocated to intravenous alteplase plus thrombectomy additionally received intravenous alteplase as early as possible after randomization. Intravenous alteplase (0·9mg/kg body weight with a maximum dose of 90mg per patient) was administered for 60 minutes with 10% of the calculated dose given as an initial bolus. Unless there were medical contraindications (e.g., ongoing bleeding), the complete dose of alteplase was administered. In both treatment arms, the use of a balloon guide catheter and/or distal aspiration catheter during thrombectomy was strongly encouraged, while intra-arterial administration of fibrinolytics was prohibited. Other concomitant treatments, medications and post-operative care were guided by the international standard of care for intravenous thrombolysis and thrombectomy.[20–22]

Outcome Measures

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 blinded 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 hours after randomization, 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 lab. 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 (eTICI)[23] score 2b50-3; complete reperfusion, defined as eTICI score 3; and time from admission to successful reperfusion. Additionally, reperfusion between initial CTA/MRA and initial digital subtraction angiography, and reperfusion between initial CTA/MRA and final digital subtraction angiography were rated with the cross-sectional eTICI (cs-eTICI, see Methods S1). This was a post-hoc analysis not prespecified in the protocol.

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

Statistical Analysis

Sample size was based on the assumption that 62·2% of patients in the control arm would be functionally independent at 90 days after randomization and a non-inferiority margin of 12%. Using the above-mentioned numbers, 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 expecting 80% of patients to 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 mothership patients. As centers had a geographically different distribution and stroke care organization differed from centers participating in SWIFT PRIME, we mixed mothership patients with 20% drip-and-ship patients for this calculation.

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 (modified Rankin scale score 0–2 control/best medical treatment: 35·5%, experimental/ thrombectomy: 60·2%, treatment effect: 24·7%, 60% preservation: 14·8%, non-inferiority margin: 9·9%).[3] The SWIFT PRIME trial was chosen as the treatment effect reference because it had very similar inclusion and exclusion criteria.[3] Owing to the wide variation of outcomes in the best medical treatment plus thrombectomy arms of the SWIFT PRIME trial,[3] the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)[1] and Randomized Trial of Revascularization with Solitaire

FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT)[24] trials, there was a concern that the projected event rate in the control arm of SWIFT DIRECT had poor precision. Another concern was that the constancy assumption might not hold in full, because technical advances (e.g., 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 ~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 performed after 202 patients had reached the primary outcome. The re-estimation was based on the frequency of patients in the control arm 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 using the one-sided lower 95% confidence limit of the Mantel-Haenszel risk difference stratified according to randomization strata. Non-inferiority would be claimed if it lay above −12% in both the intention-to-treat and per-protocol analyses. If non-inferiority had been demonstrated, 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 have been performed. No type-I error control was used for this test, as the multiple testing procedure is strictly hierarchical.

Secondary binary outcomes were analyzed using the same method, but with a two-sided 95% confidence interval (CI). Continuous variables were analyzed using linear regression with robust standard errors adjusted for randomization strata and baseline values (for the NIHSS score). The modified Rankin scale was analyzed using a proportional odds ordinal logistic regression with the treatment group and randomization strata as covariates. Time to event data were analyzed using flexible parametric survival models with the treatment group and randomization 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 randomized patients. 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 using multiple imputations (Methods S2) or censoring (for mortality). Multiple imputed data sets were used for all efficacy outcome analyses.

The primary outcome was analyzed for predefined subgroups (randomization strata, protocol version) and a post-hoc subgroup (sex) using logistic regression models with the treatment group, the subgroup and their interaction as covariates (Methods S3).

The safety population consisted of all subjects in the full analysis set who received one of the study interventions, including patients who did not undergo thrombectomy owing to pre-interventional reperfusion. Subjects were analyzed according to the treatment they actually received (as treated).

All analyses were performed by a trial statistician using STATA version 17.0 (StataCorp, TX, USA), 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 (see details in Methods S4).[25]

The study was supported by an unrestricted grant from Medtronic to the University Hospital Bern. The funder (Medtronic) has not been involved in data collation, analysis, interpretation, writing of the manuscript or the decision to submit. LB, PP and SD had full access to the data and/or verified the underlying raw data. The following authors were responsible for the decision to submit the manuscript: UF, JK, LB, JLS and JG.

Results

Study Enrollment and Characteristics of the Patients

Between November 2017 and May 2021, 423 patients at 42 centers were randomized (see Figure S1 and Table S2 for further details). Fifteen patients were excluded after randomization because they declined post-hoc consent (N=14) and one owing to an accidental web-browser randomization during the eligibility check. For each patient excluded a new patient was randomized. The trial enrolled to completion with a total of 201 patients assigned to receive thrombectomy alone and 207 patients assigned to receive intravenous thrombolysis plus thrombectomy (see Figure 1 for study flow chart). Of 408 patients, 402 received the allocated intervention. There were three cross-overs in each treatment group and other major prespecified protocol violations were documented in 64 patients (See Table S3 for details). 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 presented in Table 1 and Table S4.

Intervention and Time Metrics

The delay from arrival at the emergency department to administration of intravenous alteplase was 55 minutes (interquartile range 38–71) and the full dose was administered to 198 (96·6%) of the patients receiving intravenous alteplase (see Table S5). Catheter angiography was performed in all patients. All patients assigned to thrombectomy alone underwent thrombectomy, whereas seven patients assigned to intravenous thrombolysis plus thrombectomy did not undergo thrombectomy (in five patients due to partial or complete reperfusion, in one patient owing to failed intracranial access due to tortuous cervical vessels, and in one patient after thrombus migration following carotid puncture). Details of the thrombectomy procedure are provided in Table S6.

Primary Outcome

The primary outcome of modified Rankin scale score of 0–2 at 90 days was reached by 114 patients assigned to thrombectomy alone (57%) and 135 patients assigned to intravenous thrombolysis plus thrombectomy (65%, 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, Table 2). The non-inferiority margin of −12% was also crossed when restricting analyses to other predefined populations (Tables S7–S9). Because of failure to show non-inferiority of thrombectomy alone, all subsequent analyses were exploratory without formal type-I error control.

Secondary Outcomes

Prespecified secondary clinical efficacy outcomes and technical efficacy outcomes are shown in Table 2. At 90 days, 22 patients assigned to thrombectomy alone and 17 patients assigned to intravenous alteplase plus thrombectomy had died (risk difference 2·3%, 95% CI −3·2 to 7·8%, Figure S2). 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 prior to thrombectomy (cs-eTICI2b50-3) occurred in two patients assigned to thrombectomy alone and eight 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 (cs-eTICI2b50-3, n= 182, 91% versus n=199, 96%, risk difference −5·1%, 95% CI −10·2 to 0·0%, P=0·047). In the complete cohort, only 2 of 27 patients in whom reperfusion was not successful (cs-eTICI<2b50) were functionally independent at 90 days.

Safety

Central adjudicated symptomatic intracranial hemorrhage ($sICH_{global}$) occurred in five patients undergoing thrombectomy alone and seven 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 and those treated with intravenous alteplase plus thrombectomy (n=56, 28% versus n=54, 26%, 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 Table S10, while interventional complications and prespecified adverse events at day 1 are listed in Table S11. In five 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.

Subgroup Analyses

With the exception of age, no evidence was found of treatment effect modification (Figures S3 and S4). The primary outcome was observed comparably often in both treatment groups when considering patients aged ≥70 years (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 for interaction 0·039). The non-inferiority margin of 12% was crossed in all subgroups analyzed.

Discussion

This study compared thrombectomy alone to intravenous alteplase plus thrombectomy in lytic-eligible patients with acute ischemic stroke due to large vessel occlusion in the anterior circulation who arrived directly at stroke centers, 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 to intravenous thrombolysis plus thrombectomy in yielding functional independence at 3 months could not be demonstrated. Notably, point estimates directionally favored intravenous thrombolysis plus thrombectomy and similar outcome patterns were seen for all secondary clinical

efficacy measures. Although alteplase-associated pre-interventional reperfusion occurred infrequently, final post-interventional 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 may reflect conservative selection of ideal candidates for thrombectomy, frequent use of flow-arrest devices, and the overall high standard of care of participating centers. 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 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. No other trial comparing direct thrombectomy to intravenous alteplase plus thrombectomy found a significant difference in the rate of successful reperfusion after endovascular treatment, although all trials reported numerical differences in the same direction (i.e. favoring the intravenous alteplase plus thrombectomy arm).[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 may 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 the combined treatment with intravenous alteplase plus aspiration might have been averted and using stent-retrievers with concomitant proximal flow-arrest and/or distal aspiration seemed to translate into an overall favorable reperfusion rate in patients treated with intravenous alteplase plus thrombectomy. The difference in successful reperfusion seems mainly driven by more successful interventions as differences due to pre-interventional reperfusion are neglected by the classic TICI grading.[28] The rate of pre-interventional successful reperfusion did not differ significantly between the two treatment arms, 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 may have translated into numerical differences regarding functional outcomes, favoring the intravenous alteplase plus thrombectomy group. Consequently, the liberal margin of 12% based upon the hypothesis of a reasonable clinical comparability was not met.[19] This result aligns with the results of MR CLEAN NO IV and the SKIP trial,[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 may 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 Caucasian patients also did not demonstrate non-inferiority,[13] omitting intravenous alteplase in this population seems unjustified.

Importantly, administration of intravenous alteplase did not increase the risk of symptomatic intracranial hemorrhage, although the statistical power to detect a difference was limited by the small number of symptomatic bleedings. An individual patient meta-analysis of trials comparing intravenous alteplase with placebo or open control found that intravenous alteplase increases the risk of type 2 parenchymal hemorrhage by 5·5% (6·8 versus 13%).[29] Besides study-size-associated power considerations, the lack of a clear association of intravenous alteplase with increased bleeding risk in this study may also be associated with overall good reperfusion, which seems to protect patients from hemorrhages and hemorrhagic 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 ≥70 years, 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 certain 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 generalizability to current clinical practice.[34] 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 centers that usually administer IVT before CTA/MRA is performed. To mitigate the chances of delays, an extensive and detailed feasibility check of the participating centers was conducted to ensure that all of them could provide fast CTA acquisition directly after non-contrast CT or MRA acquisitions after FLAIR/DWI/T2*. Moreover, all centers had to provide staff for parallel consenting and randomization 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 center about how the delay associated with the requirement for a CTA/MRA before inclusion could be minimized. This included immediate acquisition of CTA and changes to MRI protocols to keep delays to a minimum. Third, the study was powered to assess a broad non-inferiority margin; pooled individual participant data level analyses aggregating completed trials are desirable to improve precision of the findings. Fourth, per-protocol analysis was limited to 339 (83%) 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 centers 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 randomized after undergoing admission MRI, which may further limit the generalizability of the data.

In conclusion, non-inferiority of thrombectomy alone when compared with intravenous alteplase plus thrombectomy in patients presenting with acute ischemic 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 manuscript was written by JK, UF, JLS and JG. Statistical analyses and drawing of figures were performed in STATA by LB. All authors contributed to data acquisition and made critical revisions to the manuscript text. LB, PP and SD had full access to the data and/or verified the underlying raw data.

Declaration of 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 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 .

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.

MM reports payment or honoraria from Boehringer Ingelheim

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 fromLAERDAL medical, Alexion, Pfizer-BMS and Stryker neurovascular.

MR reports consulting fees from Medtronic /Stryker/ Cerenovus/Philips/Apta Targets; ayment or honoraria from Ischemia View; Participation on a Data Safety Monitoring Board or Advisory Board of Sensome; 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., Truvic 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, Boheringer Ingelheim, Astra-Zeneca, Novonordisk and Medtronic; payment or honoraria (paid to IS) from Sanofi Synthé-Labo, Medtronic, Boheringer Ingelheim, Astra-Zeneca 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.

Data sharing

Data from the SWIFT DIRECT trial are currently not publicly available. The plan is to make them available in the future. A complete de-identified 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.

Acknowledgements

SWIFT DIRECT was designed by the academic investigators. The study was supported by an unrestricted grant from Medtronic to the University Hospital Bern. The funder (Medtronic) has not been involved in data collation, analysis, interpretation, writing of the manuscript or the decision to submit. Further funding was provided by intramural funds of the University Hospital of Bern, Switzerland. English language support was provided by Susan Kaplan, University Hospital Bern, Bern, Switzerland.

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Tables

Table 1. Patient baseline characteristics

	Thrombectomy alone (N = 201)	Intravenous alteplase plus thrombectomy (N = 207)
Median age – yr (IQR)	73 (64, 81)	72 (65, 81)
Female sex – no. (%)	105 (52%)	104 (50%)
Median NIHSS score (IQR) †	17 (13, 20)	17 (12, 20)
Pre-stroke score on the modified Rankin scale no. (%)‡		
0	167 (83%)	179 (86%)
1	34 (17%)	27 (13%)
4	0 (0%)	1 (0%)
Median systolic blood pressure – mmHg (IQR)§	147 (130, 160)	148 (134, 165)
Median blood glucose level – mmol/L (IQR)¶	6·5 (5·8, 7·5)	6·6 (5·8, 7·6)
Risk factors‖		
Previous ischemic stroke – no. (%)		
no	172 (86%)	181 (87%)
yes	21 (10%)	20 (10%)
unknown	8 (4%)	6 (3%)
Previous transient ischemic attack – no. (%)		

no	182 (91%)	186 (90%)
yes	7 (3%)	14 (7%)
unknown	12 (6%)	7 (3%)
History of hypertension – no. (%)		
no	75 (37%)	84 (41%)
yes	121 (60%)	118 (57%)
unknown	5 (2%)	5 (2%)
History of atrial fibrillation – no. (%)		
no	172 (86%)	176 (85%)
yes	17 (8%)	22 (11%)
unknown	12 (6%)	9 (4%)
History of hypercholesterolemia – no. (%)		
no	133 (66%)	123 (59%)
yes	60 (30%)	71 (34%)
unknown	8 (4%)	13 (6%)
Baseline imaging – no. (%)‖		
CT	105 (52%)	100 (48%)
MRI	95 (47%)	105 (51%)
both	1 (0%)	2 (1%)
Median ASPECTS – (IQR)**	8 (7, 9)	8 (7, 9)
Baseline intracranial occlusion site – no. (%)††		
ICA	57 (28%)	60 (29%)
M1	133 (66%)	136 (66%)

M2	11 (5%)	11 (5%)
Tandem lesion – n (%)§§	30 (15%)	33 (16%)
Median duration (IQR) – min		
Stroke onset to randomization¶¶	123 (99, 163)	135 (106, 171)
Median time from arrival at emergency department to intravenous alteplase‖‖	55 (38, 79)	55 (38, 71)
Median time from arrival at emergency department to groin arterial puncture	75 (60, 90)	80 (63, 101)
Start of intravenous alteplase to arterial puncture – min. (IQR)‖‖	3·0 (-56, 40)	24 (15, 35)

ICA denotes internal carotid artery, MRI magnetic resonance imaging, CT computed tomography, IQR interquartile range.

* Scores on the National Institutes of Health Stroke Scale range from 0–42, with 0 indicating no deficits and a higher score indicating more severe neurological symptoms.

† Score on the modified Rankin scale range from 0 (no symptoms) to 6 (death). Pre-stroke disability was assessed by the treating physician using information provided by the patient, healthcare records and/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.

¶ Baseline imaging modality was chosen according to the standard of care of the enrolling center.

‖ Risk factors denote known risk factors according to the medical history of the patient. This excludes de novo detection of e.g. atrial fibrillation or arterial hypertension during the acute hospital stay.

** The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) evaluates early ischemic changes in the hypoperfused territory. A score of 10 indicates absence of such changes, while for each standardized brain region in the middle cerebral artery territory that exhibits such changes one point is subtracted. ASPECTS was evaluated on non-contrast computed tomography 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 ischemic 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 Solitaire thrombectomy alone group and six patients in the intravenous alteplase plus Solitaire thrombectomy group, baseline occlusion location was rated on first invasive angiography images, because baseline imaging did not include CT/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 Solitaire thrombectomy alone group and two patients in the intravenous alteplase plus Solitaire thrombectomy group baseline occlusion location was rated on baseline imaging using a synopsis of available sequences, but CT/MR angiography was not available or of poor quality. In all other patients, baseline occlusion location was rated on CT/MR angiography images. ICA denotes internal carotid artery, while M1 and M2 refer to the first and second segment of the middle cerebral artery, respectively.

§§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 point of randomization.

¶¶ 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 (cross-over) and missing for three patients in the intravenous alteplase plus thrombectomy group (cross-over). In one of the three patients assigned to the thrombectomy alone group, who received intravenous alteplase, it was administered after arterial puncture (56 minutes after arterial puncture, noted as −56 in the table).

Table 2. Primary and Secondary Efficacy Outcomes

	Thrombectomy alone (N = 201)		Intravenous alteplase plus thrombectomy (N = 207)		Measure of effect	Adjusted effect (95% CI)†	P-value‡
Outcome	N* (imputed)		N* (imputed)				
Primary outcome							
Modified Rankin scale score 0–2 – no. (%)	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 outcomes							
Clinical efficacy							
Mortality at 90 days§	201	22 (11%)	207	17 (9%)	Risk difference	2·3% (95% CI −3·2 to 7·8%)	0·41

Median modified Rankin scale score (IQR)	201(1)	2 (1, 4)	207 (0)	2 (1, 3)	Common odds ratio (for a better outcome)	0·75 (0·53 to 1·06)	0·10
Median change in NIHSS between admission and 24h (IQR)	201 (4)	-9·0 (-14, -1·7)	207 (7)	-10 (-14, -4·0)	Mean difference	0·92 (−0·59 to 2·42)	0·23
Quality-of-life dimensions¶							
Any problems with mobility – no. (%)	178 (10)	84 (47%)	190 (7)	71 (37%)	Risk difference	7·9% (95% CI −2·5 to 18·1%)	0·14
Any problems with self-care – no. (%)	178 (11)	57 (32%)	190 (8)	55 (29%)	Risk difference	0·5% (95% CI −9·0 to 10·0%)	0·91

Any problems with usual activities – no. (%)	178 (11)	96 (54%)	190 (7)	97 (51%)	Risk difference	2·1% (95% CI −8·3 to 12·4%)	0·70
Any problems with pain/discomfort – no. (%)	178 (10)	96 (54%)	190 (9)	84 (44%)	Risk difference	9·6% (95% CI −1·2 to 20·2%)	0·082
Any problems with anxiety/depression – no. (%)	178 (13)	75 (42%)	190 (10)	84 (44%)	Risk difference	−3·1% (95% CI −13·9 to 7·8%)	0·58
Median visual analogue scale (IQR)	178 (29)	70 (50, 80)	190 (29)	70 (60, 85)	Mean difference	−4·78 (−10·0 to 0·42)	0·072
Technical efficacy							
Mean time from emergency department arrival	201 (23)	125 (119 to 131)	207 (18)	123 (118 to 128)	Restricted mean survival	2·2 (−5·8 to 10)	0·59

to successful reperfusion (95% CI) – min.					time difference		
Pre-interventional eTICI 2b50-3 ||	201 (2)	1 (0%)	207 (1)	2 (1%)	Risk difference	−0·3% (95% CI −2·0 to 1·4%)	0·71
Final eTICI2b50-3 ||	201 (3)	182 (91%)	207 (8)	199 (96%)	Risk difference	−5·1% (95% CI −10·2 to 0·0%)	0·047
Final eTICI3 ||	201 (3)	67 (33%)	207 (8)	75 (36%)	Risk difference	−3·9% (95% CI −13·4 to 5·6%)	0·41
Pre-interventional cs-eTICI 2b50-3**	201 (5)	2 (1%)	207 (7)	8 (4%)	Risk difference	−2·9% (95% CI −6·0 to 0·3%)	0·077
Final cs-eTICI 2b50-3**	201 (5)	182 (91%)	207 (7)	199 (96%)	Risk difference	−5·1% (95% CI −10·2 to 0·0%)	0·047

* Number of non-missing data.

† The analyses were stratified or adjusted using randomization strata. Crude results, a complete case analysis and analysis of a per-protocol population are presented in the Supplementary Appendix.

‡ No adjustment for multiple testing has been made for any of the secondary outcomes.

Lower than the non-inferiority margin of −12%, i.e., 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 performed. 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 (displayed in this table).

¶ Excluding 40 patients who were not alive at the day 90 assessment.

|| Grades on the extended Thrombolysis in Cerebral Infarction Scale (eTICI) range from 0 (no reperfusion) to 3 (complete reperfusion), with grades higher than 2b50 defined as successful reperfusion. Pre- and post-interventional eTICI was assessed by the imaging core lab on pre-interventional or post-interventional digital subtraction catheter angiography images.

** cs-eTICI denotes cross-sectional eTICI, referring to reperfusion grading relative to the occlusion site on baseline cross-sectional imaging. Pre- and post-interventional cs-eTICI was assessed by the imaging core lab on pre-interventional or post-interventional digital subtraction catheter angiography images and with reference to the baseline cross-sectional imaging.

Table 3. Trial Safety Outcomes

	Received thrombectomy alone (N = 201) n/N* (%)	Received intravenous alteplase plus thrombectomy (N = 207) n/N* (%)	Risk difference (95% CI)	P-value
Any intracranial hemorrhage up to 24h†	59/201 (29%)	69/205 (34%)	−4·3% (−13·2 to 4·7%)	0·39
Radiological bleeding classification‡				
SAH	16/201 (8%)	18/205 (9%)	−0·8% (−6·4 to 4·7%)	0·86
PH1	1/201 (0%)	0/205 (0%)	0·5% (−1·4 to 2·8%)	0·50
PH2	2/201 (1%)	6/205 (3%)	−1·9% (−5·3 to 1·1%)	0·28
HI1	28/201 (14%)	33/205 (16%)	−2·2% (−9·2 to 4·8%)	0·58
HI2	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 24h	1/201 (0%)	4/204 (2%)	−1·5% (−4·5 to 1·1%)	0·37
Groin hematoma (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 (0%)	5/207 (2%)	−1·9% (−5·1 to 0·7%)	0·22
Any SAE (within 90 days)**	56/201 (28%)	54/207 (26%)	1·8% (−6·8 to 10·3%)	0·74

* Number of patients with non-missing data.

† Adjudicated by the imaging core lab

‡ Adjudicated by the imaging core lab. SAH denotes subarachnoid hemorrhage, PH1 denotes parenchymal hemorrhage type 1, PH2 denotes parenchymal hemorrhage type 2, HI1 denotes hemorrhagic infarction type 1, and HI2 denotes hemorrhagic infarction type 2. Numbers do not sum up as there were four patients with SAH and HI2 and one patient with SAH and PH2.

§ $sICH_{global}$ was adjudicated by the imaging core lab and was defined as the occurrence of PH1, PH2, SAH or intraventricular hemorrhage and an increase of NIHSS of more than 4 points between admission and 24 hours post-randomization.

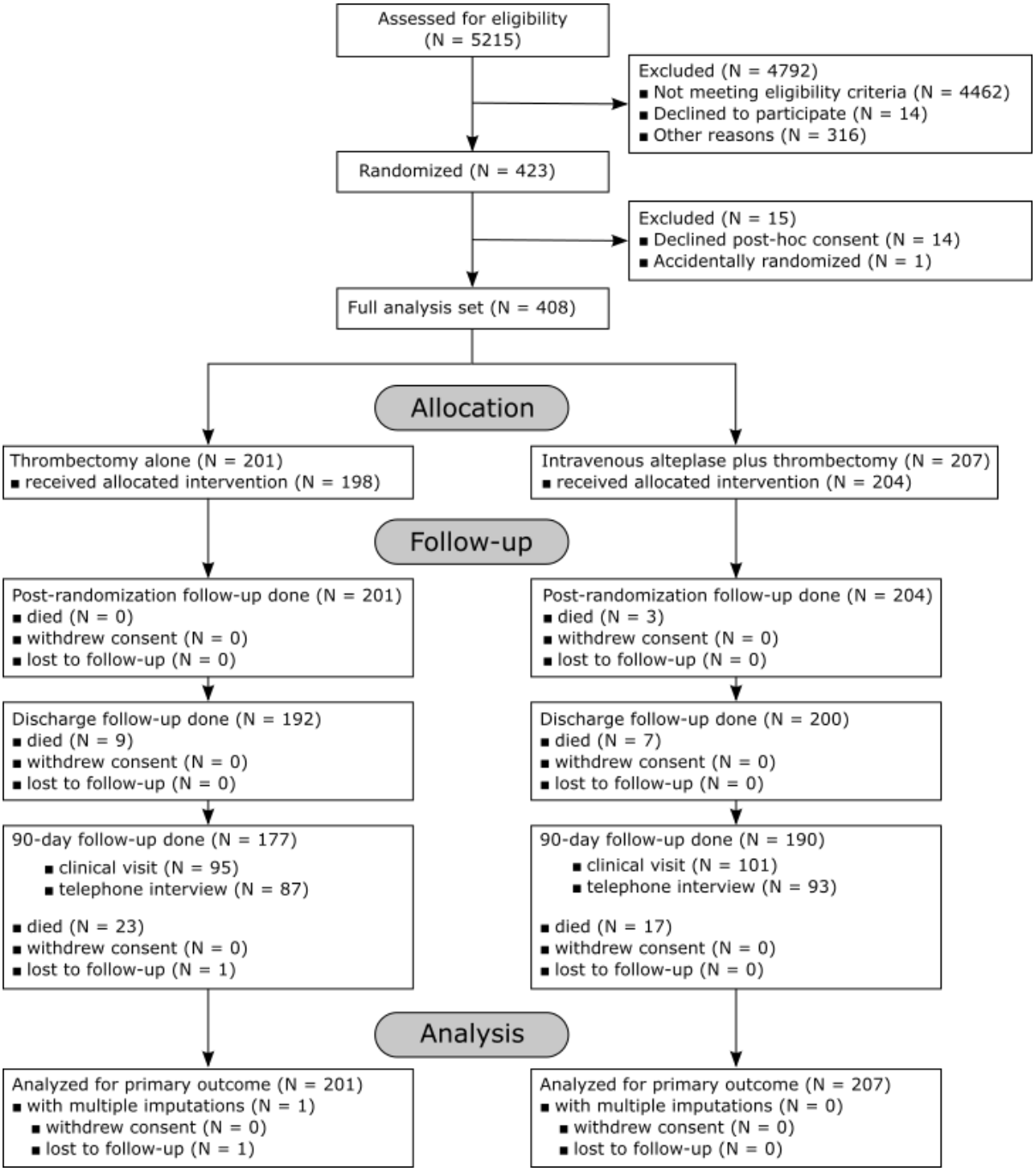
¶ $sICH_{site}$ was adjudicated by the local investigators if there was radiological evidence of intracranial hemorrhage and the patient had an increase of 4 or more points on the NIHSS compared to immediately before deterioration. The imaging core lab assigned the following radiological bleeding class to these 13 patients: 4 SAH, 1 SAH and HI2, 4 PH2, and 3 HI2. For one patient, follow-up imaging was unavailable to the imaging core lab.

** SAE denotes a serious adverse event. One patient who underwent thrombectomy alone without SAE and was lost to follow-up after 9 days is included here.

†† Or up to the time of death for the 16 patients that died earlier.

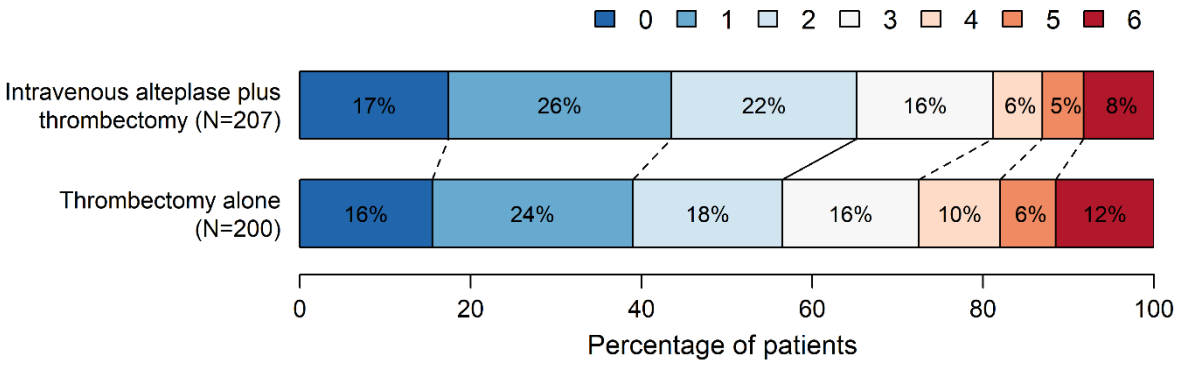
Figures

Figure 1. Study flow-chart



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/thrombectomy by the local operator (n=23), out of working hours presentation (n=41), and an individual decision by the stroke consultant to prioritize thrombolysis (n=5).

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 cut-off for functional independence (mRS 0–2). This was reached in 113 (57%) and 135 (65%) of patients assigned to thrombectomy alone, and thrombectomy combined with intravenous thrombolysis, respectively (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.