Value of intravenous thrombolysis in endovascular treatment for large-vessel anterior circulation stroke: individual participant data meta-analysis of six randomised trials

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Summary

Background Intravenous thrombolysis is recommended before endovascular treatment, but its value has been questioned in patients who are admitted directly to centres capable of endovascular treatment. Existing randomised controlled trials have indicated non-inferiority of endovascular treatment alone or have been statistically inconclusive. We formed the Improving Reperfusion Strategies in Acute Ischaemic Stroke collaboration to assess non-inferiority of endovascular treatment alone versus intravenous thrombolysis plus endovascular treatment.

Methods We conducted a systematic review and individual participant data meta-analysis to establish non-inferiority of endovascular treatment alone versus intravenous thrombolysis plus endovascular treatment. We searched PubMed and MEDLINE with the terms "stroke", "endovascular treatment", "intravenous thrombolysis", and synonyms for articles published from database inception to March 9, 2023. We included randomised controlled trials on the topic of interest, without language restrictions. Authors of the identified trials agreed to take part, and individual participant data were provided by the principal investigators of the respective trials and collated centrally by the collaborators. Our primary outcome was the 90-day modified Rankin Scale (mRS) score. Non-inferiority of endovascular treatment alone was assessed using a lower boundary of 0·82 for the 95% CI around the adjusted common odds ratio (acOR) for shift towards improved outcome (analogous to 5% absolute difference in functional independence) with ordinal regression. We used mixed-effects models for all analyses. This study is registered with PROSPERO, CRD42023411986.

Findings We identified 1081 studies, and six studies (n=2313; 1153 participants randomly assigned to receive endovascular treatment alone and 1160 randomly assigned to receive intravenous thrombolysis and endovascular treatment) were eligible for analysis. The risk of bias of the included studies was low to moderate. Variability between studies was small, and mainly related to the choice and dose of the thrombolytic drug and country of execution. The median mRS score at 90 days was 3 (IQR 1–5) for participants who received endovascular treatment alone and 2 (1–4) for participants who received intravenous thrombolysis plus endovascular treatment (acOR 0·89, 95% CI 0·76–1·04). Any intracranial haemorrhage (0·82, 0·68–0·99) occurred less frequently with endovascular treatment alone than with intravenous thrombolysis plus endovascular treatment. Symptomatic intracranial haemorrhage and mortality rates did not differ significantly.

Interpretation We did not establish non-inferiority of endovascular treatment alone compared with intravenous thrombolysis plus endovascular treatment in patients presenting directly at endovascular treatment centres. Further research could focus on cost-effectiveness analysis and on individualised decisions when patient characteristics, medication shortages, or delays are expected to offset a potential benefit of administering intravenous thrombolysis before endovascular treatment.

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Introduction

In the landmark trials on endovascular treatment for acute ischaemic stroke caused by large-vessel anterior circulation occlusion, all enrolled participants received intravenous thrombolysis if they were eligible, because intravenous thrombolysis was the standard of care at the time.[1] Consequently, when endovascular treatment was shown to be efficacious, guidelines recommended

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Research in context

Evidence before this study

Endovascular treatment for acute ischaemic stroke due to large-vessel anterior circulation occlusions was shown to be a beneficial addition to standard treatment, including intravenous thrombolysis, in eligible patients. Administration of intravenous thrombolysis before endovascular treatment is therefore recommended in international guidelines. However, its value in combination with endovascular treatment in patients admitted directly to endovascular treatment centres—ie, around 50% of all patients who are eligible for endovascular treatment—is controversial. Worldwide shortages of alteplase and tenecteplase have increased the relevance of this topic. Additionally, research on withholding ineffective treatments is gaining importance as the world population ages and health-care costs rise. We searched PubMed and MEDLINE for randomised controlled trials published from database inception to March 9, 2023, comparing endovascular treatment alone with intravenous thrombolysis plus endovascular treatment in patients eligible for both treatments presenting directly at centres capable of endovascular treatment. Search terms were "stroke", "endovascular treatment", "intravenous thrombolysis", and synonyms. We did not restrict the search by language. Six randomised clinical trials were identified. Two trials showed non-inferiority and four trials were statistically inconclusive, due in part to moderate sample sizes, resulting in wide CIs and decreased reliability of subgroup analyses. Study-level meta-analyses showed conflicting results and interpretations.

Added value of this study

This study is the first individual participant data meta-analysis comparing clinical outcomes of intravenous thrombolysis plus endovascular treatment with endovascular treatment alone in patients presenting at centres capable of endovascular treatment. Before the pooled six randomised trials, no randomised evidence existed on the benefit of intravenous alteplase in this specific population. Despite inclusion of 2313 patients, we cannot confirm non-inferiority of endovascular treatment alone (at a non-inferiority boundary of 5% difference in 90-day functional independence). Superiority of intravenous thrombolysis and endovascular treatment was also not observed.

Implications of all the available evidence

On the basis of our data, we cannot exclude possible loss of a clinically relevant effect when omitting intravenous thrombolysis in patients undergoing endovascular treatment who present directly at centres capable of endovascular treatment. Current guideline recommendations should remain in place. However, the benefit of intravenous thrombolysis in this setting is likely to be small. Moreover, including this study, no randomised evidence of benefit of intravenous thrombolysis with alteplase in patients eligible for endovascular treatment presenting directly at endovascular treatment-capable centres exists. Further research could focus on cost-effectiveness analysis and on more individualised decisions in settings where patient characteristics, shortages of medication, scarce resources, delays, or alternative effective treatments (eg, cytoprotectants) are expected to offset the potential benefit of administering intravenous thrombolysis before endovascular treatment for patients presenting directly to centres capable of endovascular treatment. The difference between the small (potential) effect size of additional intravenous thrombolysis and the large effect of endovascular treatment illustrates that intravenous thrombolysis should not prohibit, delay, or be prioritised over endovascular treatment in our population. Notably, our results are applicable to intravenous alteplase rather than tenecteplase, since only 25 patients in our population received tenecteplase. Our results do not apply to patients transferred for endovascular treatment from a primary centre.

intravenous thrombolysis before endovascular treatment for all eligible patients.[2,3] Since the approval of endovascular treatment with thrombectomy, an increasing number of patients present directly at centres capable of endovascular treatment, with registries from the USA, Europe, and China showing that this population represents at least 50% of all patients with stroke who are eligible for endovascular treatment.[4–6] The value of intravenous thrombolysis in patients with stroke who are eligible for endovascular treatment and present directly to a centre capable of endovascular treatment has been questioned. Short lytic dwell times might limit the benefits of intravenous thrombolysis, and thrombolytics are known to carry an increased risk of intracranial haemorrhage and a low chance of recanalisation in patients with large-vessel occlusions. Omitting thrombolysis in this specific population could reduce health-care costs and workflow delays.

No randomised controlled trial has established a benefit of intravenous thrombolysis with alteplase in patients eligible for endovascular treatment presenting directly at endovascular treatment-capable centres. Six clinical trials randomly assigned patients with anterior circulation large-vessel occlusions who were eligible for endovascular and intravenous treatment, and were admitted directly to an endovascular treatment centre, to receive intravenous thrombolysis with endovascular treatment or endovascular treatment alone.[7–12] Most of these trials aimed to establish non-inferiority of endovascular treatment alone compared with intravenous thrombolysis and endovascular treatment by use of non-inferiority margins ranging from 7% to 12% absolute difference in rates of functional independence at 3 months after stroke.[7–12] Two trials showed non-inferiority of endovascular treatment alone, and the others were statistically inconclusive. A benefit of

intravenous thrombolysis was also not observed. Since the trials had moderate sample sizes and wide CIs around the effect estimates, data pooling could provide more precise treatment effect estimates.[13] To address these issues, we conducted an individual participant data meta-analysis of all published randomised controlled trials comparing endovascular treatment alone with intravenous thrombolysis plus endovascular treatment. Additionally, we aimed to explore effect heterogeneity in specific subgroups of patients who might benefit from tailored therapeutic approaches.

Methods

Search strategy and selection criteria

We conducted a systematic review and individual participant data meta-analysis to establish non-inferiority of endovascular treatment alone versus intravenous thrombolysis plus endovascular treatment. Two authors (MK and FC) did a systematic search for randomised controlled trials comparing endovascular treatment alone with intravenous thrombolysis plus endovascular treatment for acute ischaemic stroke due to large-vessel occlusion of the anterior circulation, in patients presenting directly to a centre capable of endovascular treatment. Published studies were identified from PubMed and MEDLINE using search terms for "stroke", "endovascular treatment', "intravenous thrombolysis", and synonyms from database inception up to March 9, 2023. The full search strategy is shown in the appendix (p 11). No limitations on language or publication date were set. Inclusion criteria for the systematic review and meta-analysis were the same. No conflicts arose over inclusion. The authors of the identified trials agreed to participate in an individual participant data meta-analysis as part of the Improving Reperfusion Strategies in Acute Ischaemic Stroke (IRIS) collaboration.

Ethical board approval was obtained from participating centres or the central national ethics committees for each trial, as reported in the respective publications. All patients or proxies provided consent for data collection and usage in the original trials; all data were anonymised before pooling.

Data analysis

Original participant data were extracted by on-site investigators from the databases of each of the trials. Data were collated centrally by independent researchers (FC, MK, KMT, DN, and HFL), and crosschecked with the trial publications. One collaborator (FC) together with two statisticians (HFL and DN) performed the analyses after database closure. Masked core-laboratory analysis was performed on a study level.

Our prespecified primary outcome was functional outcome at 90 days after stroke as measured by the modified Rankin Scale (mRS; ranging from 0 for no residual symptoms to 6 for death), analysed with ordinal logistic regression. Prespecified secondary outcomes were rates of dichotomised functional outcomes (mRS 0–1 *vs* 2–6; mRS 0–2 [ie, functional independence] *vs* 3–6; mRS 0–3 *vs* 4–6), National Institutes of Health Stroke Scale (NIHSS) score at 3–7 days (or at discharge, if earlier), early recanalisation (ie, absence of treatable occlusion or reperfusion defined by an expanded thrombolysis in cerebral infarction [eTICI][14,15] score of 2b–3 on first angiography run compared with occlusion on baseline CT angiography or magnetic resonance angiography), successful reperfusion (eTICI score 2b–3 *vs* 0–2a), and near-complete reperfusion (2c–3 *vs* 0–2b). Safety outcomes were mortality, intracranial haemorrhage (ie, any subtype), and symptomatic intracranial haemorrhage, according to the Heidelberg Bleeding Classification (assessed by each individual trial, appendix p 25).[16]

Individual patient data were extracted for clinical and imaging baseline data, intervention details, and outcomes (appendix pp 12–13).

Data analysis was conducted after online publication of the statistical analysis plan (appendix pp 6–10) on Oct 7, 2022.[17] Between-trial differences in inclusion and treatment strategies were assessed qualitatively (appendix p 20).

We performed a one-step meta-analysis of individual participant data using a reasonable comparability framework to test whether endovascular treatment alone could be considered non-inferior to intravenous thrombolysis plus endovascular treatment.[18] In line with the original trials, we followed a non-inferiority design because differences in outcome with or without intravenous thrombolysis were expected to be small in the face of potential other (eg, logistical) benefits of omitting thrombolysis. Our non-inferiority boundary was defined before data pooling as an absolute difference in the proportion of patients reaching functional independence at 90 days not higher than 5%, based on an international survey and the European Stroke Organisation–European Society for Minimally Invasive

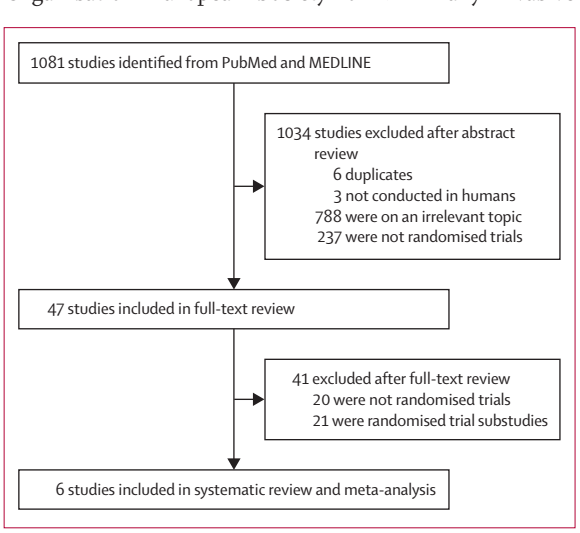

Figure 1: **Study selection**

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See **Online** for appendix

Neurological Therapy guidelines.[2,19] On the basis of the observed pooled rate of functional independence in our population control group, a 5% decrease in functional independence would be analogous to a non-inferiority margin of 0·82. Non-inferiority would be concluded if the lower bound of the 95% CI (two-sided) around the adjusted common odds ratio for ordinal mRS shift analysis was higher than 0·82.

	Endovascular treatment alone (n=1153)	Intravenous thrombolysis plus endovascular treatment (n=1160)
Demographic characteristics		
Age, years	71 (62–78)	70 (62–78)
Male	639 (55·4%)	649 (55·9%)
Female	514 (44·6%)	511 (44·1%)
Past medical history		
Atrial fibrillation	459/1150 (39·9%)	442 (38·1%)
Hypertension	643/1148 (56·0%)	675/1154 (58·5%)
Diabetes	162/1007 (16·1%)	185/1016 (18·2%)
Ischaemic stroke	161/1145 (14·1%)	161/1154 (14·0%)
Cause of stroke		
Cardioembolism	488 (42·3%)	489 (42·2%)
Large artery atherosclerosis	227 (19·7%)	203 (17·5%)
Other or undetermined	438 (38·0%)	468 (40·3%)
Baseline modified Rankin Scale score		
0–2	1141 (99·0%)	1146 (98·8%)
>2	11 (1·0%)	13 (1·1%)
Clinical characteristics		
Baseline NIHSS score*	16 (12–20)	16 (12–21)
Median systolic blood pressure, mm Hg†	148 (131–164)	148 (131–167)
Median glucose concentration, mmol/L‡	6·7 (5·8–8·0)	6·8 (5·9–8·2)
Imaging characteristics		
ASPECTS§	9 (7–10)	9 (7–10)
Cervical carotid tandem lesion¶	179/1131 (15·8%)	161/1136 (14·2%)
Baseline occlusion location		
Internal carotid artery	321/1137 (28·2%)	302/1154 (26·2%)
Middle cerebral artery (M1 or M2)	816/1137 (71·8%)	852/1154 (73·8%)
Treatment details and process times		
Time from stroke onset to random assignment, min	134 (96–182)	144 (98–193)
Time from stroke onset to needle, min‖	134 (119–175)	151 (105–200)
Time from stroke onset to arterial puncture, min**	166 (127–220)	180 (135–229)
Time from needle to arterial puncture, min††	18 (−31 to 65)	25 (15–39)
Tenecteplase‡‡	0	25 (2·2%)

Data are median (IQR) or n (%). ASPECTS=Alberta Stroke Program Early CT Score. NIHSS=National Institutes of Health Stroke Scale. *Data were missing for two participants from the endovascular treatment group and one participant from the intravenous thrombolysis plus endovascular treatment group. †Data were missing for 137 participants in the endovascular treatment group and 142 participants in the intravenous thrombolysis plus endovascular treatment group. ‡Data were missing for 155 participants in the endovascular treatment group and 159 participants in the intravenous thrombolysis plus endovascular treatment group. §Data were missing for 24 participants in the endovascular treatment group and 19 participants in the intravenous thrombolysis and endovascular treatment group. ¶As defined by individual trials. ‖Data were available due to crossover or rescue intravenous thrombolysis in 20 participants in the endovascular treatment group and data were missing for 32 participants in the intravenous thrombolysis plus endovascular treatment group. **Data were missing in 24 participants in the endovascular treatment group and 25 participants in the intravenous thrombolysis plus endovascular treatment group. ††Based on the difference between onset to arterial puncture times and onset to needle times. Data were available due to crossover or rescue (ie, after unsuccessful endovascular reperfusion) intravenous thrombolysis in 14 participants in the endovascular treatment group (for whom time from onset to needle was longer than time from onset to arterial puncture in five participants) and data were missing for 47 participants in the intravenous thrombolysis plus endovascular treatment group. ‡‡One patient in the intravenous thrombolysis plus endovascular treatment group from DIRECT-MT[7] received intravenous urokinase.

Table 1: **Baseline characteristics of participants in individual pooled patient data**

Between-trial differences were accounted for with mixed-effects models with a term for random intercept and random slope for treatment effect per study. All analyses were adjusted for age, baseline NIHSS score, baseline Alberta Stroke Program Early CT Score (ASPECTS), atrial fibrillation (including clinical history and de novo cases), occlusion location, time from symptom onset to random assignment to a treatment group, and mRS score before stroke. All results were presented as the effect estimate appropriate to the type of outcome, with 95% CIs. Missing data for covariates and outcome variables were imputed with multiple imputation using five imputations, results of which were pooled according to Rubin's rules (appendix pp 6–10). For descriptive results, only non-imputed data are reported.

We conducted prespecified subgroup analyses to assess potential treatment effect heterogeneity in the primary outcome for sex, age (ie, 18–64 years *vs* 65–79 years *vs* ≥80 years), time from onset to random assignment to a treatment group and time from onset to arterial puncture (ie, tertiles), atrial fibrillation (including clinical history and de novo cases), ASPECTS (0–5 *vs* 6–10), NIHSS score (ie, tertiles), tandem carotid lesion, and occlusion location (ie, internal carotid artery *vs* middle cerebral artery M1 or M2 segment). For the subgroup analysis, to avoid the risk of ecological bias, we first assessed within-trial effects.[20] These interaction estimates were then combined using a mixed-effects meta-analytical model.[21] Reported interaction p values are two-sided. Interpretation and assessment of the likelihood of true heterogeneity was done according to the Instrument to assess the Credibility of Effect Modification Analyses guidelines.[22]

All analyses were performed in the intention-to-treat population, defined by the randomisation treatment from each trial, excluding only patients with basilar stroke because only one study reported data for participants with basilar stroke. We also reported prespecified per-protocol results for a population of patients from the intravenous thrombolysis plus endovascular treatment group who received intravenous thrombolysis before endovascular treatment, and patients from the endovascular treatment group who did not receive intravenous thrombolysis before endovascular treatment. Patients who received intravenous thrombolysis after unsuccessful endovascular reperfusion according to trial protocol were included in the per-protocol population (appendix pp 6–10).

Additional prespecified sensitivity analyses were conducted in patients from trials that randomly assigned patients to receive alteplase 0·9 mg/kg (excluding those who received 0·6 mg/kg alteplase, those who received tenecteplase, and those who received urokinase) in the intention-to-treat and per-protocol population.

Two post-hoc as-treated analyses were conducted in patients who received thrombolysis before or after endovascular treatment versus patients who did not receive thrombolysis before or after endovascular treatment, and in those receiving thrombolysis before endovascular treatment versus patients who did not receive thrombolysis before endovascular treatment (ie, excluding those receiving rescue thrombolysis). Finally, for illustration purposes, we conducted a prespecified analysis to calculate predicted probabilities of functional independence for an average patient (ie, aged 71 years and with 138 min between onset and being randomly assigned to a treatment group, baseline NIHSS of 16, occlusion location of middle cerebral artery M1 segment or higher, no previous history of atrial fibrillation, baseline ASPECTS of 9, and baseline mRS of 0) based on the medians and modes of the applicable covariates. The difference in the predicted probabilities of reaching functional independence for the average patient in each of the treatment groups is reported as an absolute risk difference with a 95% CI.

All analyses were conducted using R (version 4.2.1). This study is reported in accordance with the PRISMA guidelines[23] for individual patient data meta-analyses (appendix pp 16–18) and was registered with PROSPERO (CRD42023411986). The statistical analysis plan is available online.[17]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We screened 1081 articles and identified six randomised clinical trials for inclusion in the systematic review and meta-analysis: DIRECT-MT,[7] DEVT,[8] SKIP,[9] MR CLEAN-NO IV,[10] SWIFT DIRECT,[11] and DIRECT-SAFE[12] (figure 1). The six trials included 2334 participants and were conducted across 15 countries: China, Japan, Canada, Australia, New Zealand, Viet Nam, and countries in Europe (appendix p 19). Only patients with occlusions of the anterior circulation were enrolled in the trials, except for DIRECT-SAFE, which included 21 patients with basilar artery occlusion. We excluded patients with basilar artery occlusion from our meta-analysis, resulting in the inclusion of 2313 patients with stroke due to anterior occlusions. 1153 patients were assigned to endovascular treatment alone (intervention population) and 1160 to intravenous thrombolysis plus endovascular treatment (active control population). All trials used intravenous alteplase as a lytic (dose 0·9 mg/kg; 0·6 mg/kg in SKIP), except for in 25 patients in DIRECT-SAFE, who received intravenous tenecteplase (0·25 mg/kg), and one patient in DIRECT-MT, who received intravenous urokinase. Full drug administration details are shown in the appendix (p 20). In accordance with international guidelines, after the start of intravenous thrombolysis, all patients proceeded directly to endovascular treatment without waiting for thrombolysis effect. Stent retrievers were the recommended first-line endovascular treatment approach in the DIRECT-MT, MR CLEAN-NO IV, and SWIFT DIRECT trials, and the other trials left the choice of materials to the interventionists.

The median participant age was 71 years (IQR 62–78); 1288 (55·7%) participants were men and 1025 (44·3%) were women (table 1). Median time from symptom onset to arterial puncture was 14 min longer in the intravenous thrombolysis plus endovascular treatment group than in the endovascular treatment group (p=0·0009). Baseline characteristics varied between trials (appendix pp 22–24).

In total, 65 (2·8%) of 2313 patients did not undergo endovascular treatment, of which 33 patients were randomly assigned to receive endovascular treatment alone. 40 (3·5%) of 1153 patients who were randomly assigned to receive endovascular treatment alone also received intravenous thrombolysis. Of the 1160 patients who were randomly assigned to receive intravenous thrombolysis plus endovascular treatment, 24 (2·1%) did not receive thrombolysis. Three (0·1%) of 2313 participants had missing 90-day mRS scores.

Outcomes were similar between the treatment groups (figure 2), but the non-inferiority boundary was crossed for our primary outcome of mRS shift (table 2). Early recanalisation occurred in fewer patients in the endovascular treatment group than in the intravenous thrombolysis plus endovascular treatment group. Successful reperfusion at the end of endovascular treatment was more common in patients receiving intravenous thrombolysis plus endovascular treatment. Patients in the group that received endovascular treatment alone had a significantly lower occurrence of any intracranial haemorrhage than patients who received intravenous thrombolysis plus endovascular treatment. There was no significant difference in symptomatic intracranial haemorrhage or 90-day mortality (table 3).

In the prespecified subgroup analyses, no evidence of treatment effect heterogeneity was found for sex, age,

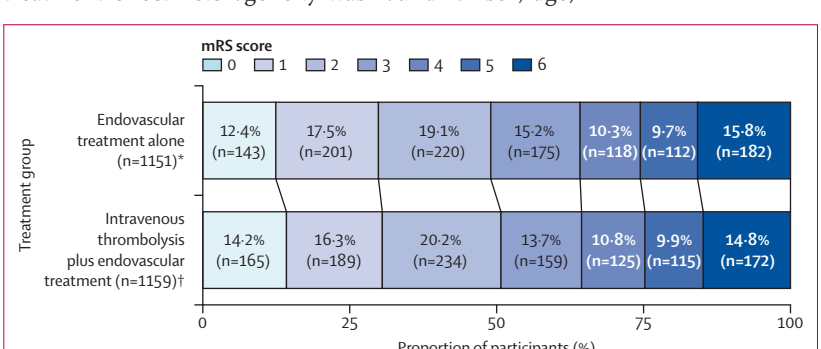

Figure 2: **Distribution of mRS scores at 90 days**
mRS=modified Rankin Scale. *Data were missing for two of 1153 participants in the endovascular treatment group. †Data were missing for one of 1160 participants in the intravenous thrombolysis plus endovascular treatment group.

	Endovascular treatment alone (n=1153)	Intravenous thrombolysis plus endovascular treatment (n=1160)	Effect measure	Unadjusted value (95% CI)	Adjusted value* (95% CI)
mRS score at 90 days (shift analysis, primary outcome)†	3 (1–5)	2 (1–4)	Common odds ratio	0·92 (0·78 to 1·09; p=0·33)	0·89 (0·76 to 1·04; p=0·14)‡
mRS score 0–1	344/1151 (29·9%)	354/1159 (30·5%)	Odds ratio	0·97 (0·79 to 1·19; p=0·75)	0·92 (0·75 to 1·13; p=0·43)
mRS score 0–2	564/1151 (49·0%)	588/1159 (50·7%)	Odds ratio	0·92 (0·77 to 1·10; p=0·34)	0·88 (0·73 to 1·07; p=0·20)
mRS score 0–3	739/1151 (64·2%)	747/1159 (64·5%)	Odds ratio	0·94 (0·75 to 1·17; p=0·56)	0·93 (0·74 to 1·18; p=0·55)
NIHSS score at 3–7 days (or at discharge if earlier)	5 (1–14)	5 (1–13)	Beta coefficient	0·07 (−0·06 to 0·19; p=0·29)	0·10 (−0·01 to 0·20; p=0·067)
Early recanalisation§	19/1108 (1·7%)	45/1125 (4·0%)	Odds ratio	0·39 (0·17 to 0·93; p=0·033)	0·41 (0·18 to 0·92; p=0·031)
Final reperfusion					
eTICI score 2b–3	921/1093 (84·3%)	973/1101 (88·4%)	Odds ratio	0·63 (0·46 to 0·86; p=0·0042)	0·62 (0·45 to 0·86; p=0·0038)
eTICI score 2c–3	587/1093 (53·7%)	638/1101 (57·9%)	Odds ratio	0·83 (0·67 to 1·03; p=0·087)	0·83 (0·67 to 1·03; p=0·094)

Data are median (IQR) or n/N (%), unless otherwise stated. eTICI=expanded thrombolysis in cerebral infarction. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. *Adjusted for age (in years), Alberta Stroke Program Early CT Score at baseline, atrial fibrillation, occlusion location based on angiographic imaging at baseline, NIHSS score at baseline, pre-stroke mRS score, and time from stroke onset to random assignment to a treatment group (in min). †Data were missing for two participants in the endovascular treatment group and one participant in the intravenous thrombolysis plus endovascular treatment group. The common odds ratio is for 1-point improvement in mRS score. ‡For the primary outcome, we report one-sided p values for non-inferiority, for both the adjusted and unadjusted analyses. All other p values are two-sided, reflecting a test for superiority of direct endovascular treatment versus intravenous thrombolysis plus endovascular treatment. §Defined as absence of treatable occlusion, or reperfusion eTICI 2b–3 as compared with baseline CT angiography or magnetic resonance angiography occlusion, on first run digital subtraction angiography imaging for endovascular treatment.

Table 2: **Efficacy outcomes in the pooled data for the intention-to-treat population**

	Endovascular treatment alone (n=1153)	Intravenous thrombolysis plus endovascular treatment (n=1160)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Symptomatic intracranial haemorrhage†	50/1152 (4·3%)	63/1156 (5·4%)	0·73 (0·47–1·11; p=0·14)	0·73 (0·46–1·14; p=0·16)
Any intracranial haemorrhage	355/1127 (31·5%)	407/1130 (36·0%)	0·82 (0·67–0·99; p=0·043)	0·82 (0·68–0·99; p=0·040)
Mortality at 90 days	182/1151 (15·8%)	172/1159 (14·8%)	1·09 (0·84–1·40; p=0·52)	1·07 (0·83–1·39; p=0·59)

Data are n/N (%), unless otherwise stated. *Adjusted for age (in years), Alberta Stroke Program Early CT Score at baseline, atrial fibrillation, occlusion location based on angiographic imaging at baseline, National Institutes of Health Stroke Scale score at baseline, pre-stroke modified Rankin Scale score, and time from stroke onset to random assignment to a treatment group (in min). †Scored according to the Heidelberg Bleeding Criteria.

Table 3: **Safety outcomes at 90 days after stroke in the pooled data for the intention-to-treat population**

time from stroke onset to arterial puncture, ASPECTS, baseline NIHSS score, previous history of atrial fibrillation, tandem carotid lesion, or occlusion location (figure 3). A significant treatment effect interaction was identified for time from onset to random assignment to a treatment group ($p_{interaction}$=0·03), favouring omitting intravenous thrombolysis in patients presenting with longer times between symptom onset and randomisation.

The risk of bias of the included studies was low to moderate (appendix p 14). Variability between studies was small and mainly related to the choice and dose of the thrombolytic drug and country of execution. There was no statistical heterogeneity between trials. In sensitivity analyses, we excluded 204 patients who received 0·6 mg/kg alteplase, 25 who received tenecteplase (0·25 mg/kg), and one patient from DIRECT-MT who received urokinase of unknown dose. The per-protocol and sensitivity analyses supported the main analysis results observed in the intention-to-treat population (appendix pp 29–33), except for one post-hoc as-treated analysis, which showed a small but significant benefit of intravenous thrombolysis (appendix p 33).

For an average patient, the estimated difference in probability of reaching functional independence at 90 days when omitting intravenous thrombolysis was −2·5% (95% CI −6·5% to 1·0%).

Discussion

We did not establish non-inferiority of endovascular treatment alone compared with intravenous thrombolysis plus endovascular treatment for patients presenting directly at centres capable of endovascular treatment. Differences in functional outcomes between treatment groups were small and not significant. Despite a sample size of 2313 patients, the superiority of intravenous thrombolysis plus endovascular treatment was also not shown in this population. Fewer patients who were randomly assigned to receive endovascular treatment alone had successful reperfusion and any intracranial haemorrhage than did patients who were assigned to receive intravenous thrombolysis plus endovascular treatment. No significant differences were observed in symptomatic intracranial haemorrhage or mortality. Treatment effect heterogeneity was observed for time from onset to random assignment to a treatment group,

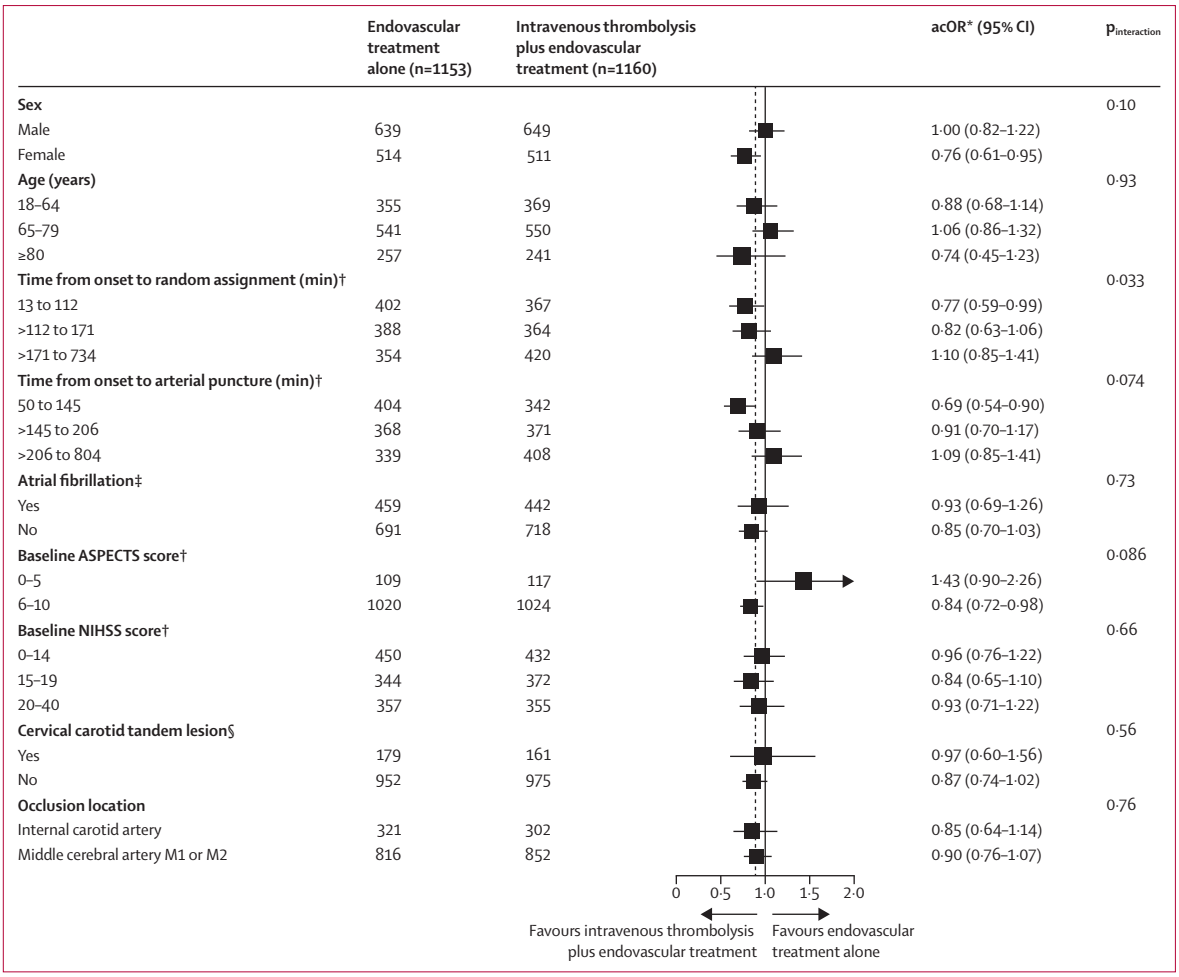

Figure 3: **Adjusted treatment effect for a 1-point shift in 90-day modified Rankin Scale score towards improved outcome, for prespecified subgroups**
acOR=adjusted common odds ratio. ASPECTS=Alberta Stroke Program Early CT Score. NIHSS=National Institutes of Health Stroke Scale. *Adjusted for age (in years), baseline ASPECTS, atrial fibrillation, occlusion location based on angiographic imaging at baseline, baseline NIHSS score, pre-stroke mRS score, and time from stroke onset to random assignment to a treatment group (in min; except for the arterial puncture subgroup analysis, where onset to random assignment was not included). The adjustment variable time to random assignment was excluded from the model estimating the $p_{interaction}$ for the onset to arterial puncture variable due to significant collinearity. †Interaction term based on continuous variable. ‡Clinical history or de novo cases. §As defined by individual trials.

with longer times favouring endovascular treatment alone, but significance for this interaction should be interpreted with caution given the number of tests performed.

The observed difference in the proportion of participants with mRS score 0–2 after intravenous thrombolysis before endovascular treatment was small (1·7%; table 3), especially when compared with the effect of endovascular treatment itself (approximately 20%).[1] Given that every hour of delay to endovascular treatment results in approximately 6% less functional independence,[24] delaying endovascular treatment by 15 min to administer intravenous thrombolysis (eg, actively lowering blood pressure or checking coagulation status) could render intravenous thrombolysis useless. For illustration purposes, our observed treatment effect for intravenous thrombolysis plus endovascular treatment roughly translates to one additional patient reaching functional independence for every 57 patients treated with thrombolysis, compared with approximately three patients for endovascular treatment. Intravenous thrombolysis should not delay or prohibit endovascular treatment in populations with anterior circulation occlusions who present to an endovascular-capable centre and are eligible for both treatments. The difference between the proportion of patients with mRS 0–1 at 90 days who received thrombolysis and those who received endovascular treatment alone was also smaller than the difference between people who received intravenous alteplase versus placebo in the general stroke population (ie, without a confirmed large vessel occlusion): 0·6% versus 6·8% difference in the 4·5 h time window.[25] Finally, the effect size of intravenous thrombolysis in the setting of endovascular treatment is considerably smaller than that suggested by observational data: an

absolute increase in functional independence of approximately 10% in favour of intravenous thrombolysis, a treatment effect excluded by our data (1·7%; table 3; predicted difference in probability of functional independence of –2·5% [95% CI –6·5 to 1·0] for the average patient).[26] This difference in results stresses that observational data are inappropriate for answering this research question due to confounding by indication.

The CIs around our effect estimate were wide, which could indicate presence of treatment effect heterogeneity for patient subgroups. A significant interaction was identified for time from onset to random assignment to a treatment group, favouring lytic administration when patients presented earlier but, given the number of subgroup tests performed, this finding should be interpreted with caution. Notably, although not significant, we observed improved outcomes for patients with lower ASPECTS who were randomly assigned to endovascular treatment alone. No other significant interaction or apparent trends were observed, including for the subgroups of carotid tandem lesions and intracranial occlusion location, in contrast to the subgroup analyses of some of the individual trials.[7–12] Further studies could investigate treatment effect heterogeneity among subgroups in more detail. If relevant subgroups can be identified, then individualised decisions can be made in settings where patient characteristics, shortages of medication, or delays are expected to offset the potential benefit of administering intravenous thrombolysis before endovascular treatment.[13] Furthermore, cost-effectiveness analysis could help to define the value of administering intravenous thrombolysis to patients presenting directly to centres capable of endovascular treatment. This analysis is especially relevant to systems in which patients pay for their own health care, as evidenced by an international panel of patients and caregivers that showed an overwhelming preference for endovascular treatment alone, particularly in countries where the cost of thrombolytic medication was considered prohibitive.[27]

Before the six randomised controlled trials in this pooled analysis took place, no randomised trials had evaluated the value of intravenous thrombolysis with alteplase in patients who received endovascular treatment after presenting at centres capable of endovascular treatment. A benefit of thrombolysis with alteplase had been shown only in patients who did not undergo endovascular treatment, because the trials were performed before endovascular treatment was shown to be efficacious. Hence, intravenous thrombolysis is recommended due to the historical order in which treatments were shown to be effective. In such a scenario, following a non-inferiority study design can delay or prevent the removal of treatments in new clinical context populations for which no proof of benefit exists, particularly if strict non-inferiority margins are required.[28–30] In non-inferiority studies, conclusions are based on the non-inferiority margin that should correspond to the maximum acceptable loss of effect in exchange for alternative benefits of the investigated treatment. Although strict margins are important, they demand large sample sizes to limit the uncertainty of treatment effect.[28] As an example, showing non-inferiority at a 5% margin and assuming our studied treatments were truly equal would require a sample size of approximately 3500 patients. We therefore suggest that if enough doubt exists about the true benefit of a commonly used treatment to warrant a randomised controlled trial, trialists should consider designing studies to prove superiority of the active standard treatment compared with no treatment, rather than non-inferiority of no treatment.

In the field of cardiology, the role of intravenous thrombolysis after approval of percutaneous coronary interventions was decided by an absence of superiority for main outcomes combined with higher rates of complications in patients receiving combined treatments instead of direct percutaneous intervention.[31] Thrombolytics are still recommended for individuals who cannot undergo immediate percutaneous intervention, but direct endovascular treatment became the preferred approach for eligible patients presenting at capable centres. Although the different conclusions for these apparently similar clinical situations might purely be a consequence of the chosen study design and which treatment was considered to be the standard, our results do not exclude the possibility that the effect of intravenous thrombolysis for the heart and brain are not exactly equal.

Overall, our study represents the highest quality data available for the value of intravenous thrombolysis administration before endovascular treatment in patients presenting directly to endovascular treatment centres. Few patients were lost to follow-up or crossed over to the other treatment group. Missing baseline data were sparse and accounted for in the analyses using multiple imputation methods. Both predominantly White and eastern Asian populations were represented, improving generalisability. Furthermore, the individual patient data allowed statistical adjustment for potential between-trial bias, covariate adjustment to increase statistical power, and a unique opportunity to investigate potential treatment effect heterogeneity in patient subgroups.

Our study has several limitations. First, our study population included only patients who presented directly at endovascular treatment centres and, therefore, our findings apply only to this specific population; however, patients who present directly to these centres constitute about 50% of all patients who are eligible for endovascular treatment in many stroke registries.[4–6] Second, no central rereading of neuroimaging was performed, necessitating redefinition of some variables so that they could be merged, which resulted in some loss of detail

(eg, M1 and M2 occlusions were grouped together). However, the most important imaging outcomes (eg, reperfusion grade and intracranial haemorrhage) were scored similarly across trials by independent core laboratories. Third, some heterogeneity existed regarding the lytic administered in the control groups; however, this difference affected few patients. In the SKIP trial (n=204), the approved standard dose for Japan was given (0·6 mg/kg rather than 0·9 mg/kg, which is used elsewhere in the world). In the DIRECT-SAFE trial, 25 patients received intravenous tenecteplase (0·25 mg/kg). In the DIRECT-MT trial, one patient received intravenous urokinase. Prespecified sensitivity analyses excluding these patients yielded similar results to the main analysis. Importantly, too few patients were treated with intravenous tenecteplase to allow for any meaningful analysis in the tenecteplase subgroup. Previous studies suggested a larger effect of tenecteplase on large-vessel occlusions,[32] but this finding was not replicated in a randomised controlled trial published in 2023.[33] Fourth, the median time window from intravenous thrombolysis administration to arterial puncture in the combined treatment group was 25 min (IQR 15–39), potentially preventing intravenous thrombolysis reaching its full effect. However, the length of this time period is not likely to have biased the results towards the direct endovascular treatment group, because a natural result of workflow improvements is to shorten treatment times. Imaging acquisition before random assignment of participants to a treatment group and the randomisation process itself did not cause substantial delays compared with clinical practice.[4] Fifth, several secondary outcomes were assessed without adjustment for multiplicity, so significant results might constitute type I error. Finally, conclusions of the original randomised controlled trials ranged from clear non-inferiority at the set margins[7,8] to inconclusive findings with varying degrees of treatment effect in the combined treatment groups.[9–12] Our observation that longer times from onset to random assignment to a treatment group were associated with a smaller effect of combined treatment seems to partly explain the observed differences, since patients tended to present later in the DEVT and DIRECT-MT trials, which established non-inferiority. However, the number of tested interactions necessitate caution in interpreting these results. The even spread of effect estimates of the individual trials around our pooled estimate also points to random sampling variation across trials being a potential underlying explanation.

In conclusion, this international individual participant data meta-analysis did not establish non-inferiority of endovascular treatment alone compared with intravenous thrombolysis plus endovascular treatment in patients eligible for both treatments presenting at centres capable of endovascular treatment. Differences in clinical outcomes were small. Despite inclusion of 2313 patients, superiority of intravenous thrombolysis plus endovascular treatment was also not shown in this population. The difference between the small potential effect size of intravenous thrombolysis and the large effect of endovascular treatment shows that intravenous thrombolysis should not prohibit, delay, or be prioritised over endovascular treatment in our population. Further research could focus on the cost-effectiveness and on individualised decisions in settings where patient characteristics, shortages of medication, or delays are expected to offset the potential benefit of administering intravenous thrombolysis before endovascular treatment.

Contributors

CBM, FC, JG, JL, YBR, UF, MK, KMT, JK, and PY prepared the first draft of the report after discussion with all authors on the results from the prespecified analyses. The IRIS collaboration was conceptualised by CBM, YBR, KK, KS, ZM, PM, BY, YZ, PY, JL, QY, RGN, KMT, MK, WZ, JG, and UF. Data collection and study organisation was directly coordinated by FC, MK, KMT, and JK. The prespecified statistical analysis plan was written by KMT, MK, FC, HFL, CBM, DN, and YBR with input from all other authors. Data pooling and statistical analysis was conducted by FC and DN with input from LAR, KMT, MK, and HFL. FC, KMT, MK, and DN accessed and verified the underlying data reported in this manuscript. All authors participated in patient enrolment, data collection, curation of the pooled data, and critically reviewed the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Data from the IRIS pooling are currently not publicly available but are planned to be made available in the future. A deidentified dataset and data dictionary will be made accessible. The timing of this availability and criteria for gaining access have not been determined.

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References

1 Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; **387:** 1723–31.
2 Turc G, Tsivgoulis G, Audebert HJ, et al. European Stroke Organisation (ESO)–European Society for Minimally Invasive Neurological Therapy (ESMINT) expedited recommendation on indication for intravenous thrombolysis before mechanical thrombectomy in patients with acute ischemic stroke and anterior circulation large vessel occlusion. *J Neurointerv Surg* 2022; **14:** 209–27.
3 Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019; **50:** e344–418.
4 Compagne KCJ, Kappelhof M, Hinsenveld WH, et al. Improvements in endovascular treatment for acute ischemic stroke: a longitudinal study in the MR CLEAN Registry. *Stroke* 2022; **53:** 1863–72.
5 Froehler MT, Saver JL, Zaidat OO, et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the STRATIS Registry (Systematic Evaluation of Patients Treated with Neurothrombectomy Devices for Acute Ischemic Stroke). *Circulation* 2017; **136:** 2311–21.
6 Tong X, Wang Y, Fiehler J, et al. Thrombectomy versus combined thrombolysis and thrombectomy in patients with acute stroke: a matched-control study. *Stroke* 2021; **52:** 1589–600.
7 Yang P, Zhang Y, Zhang L, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020; **382:** 1981–93.
8 Zi W, Qiu Z, Li F, et al. Effect of endovascular treatment alone *vs* intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA* 2021; **325:** 234–43.
9 Suzuki K, Matsumaru Y, Takeuchi M, et al. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA* 2021; **325:** 244–53.
10 LeCouffe NE, Kappelhof M, Treurniet KM, et al. A randomized trial of intravenous alteplase before endovascular treatment for stroke. *N Engl J Med* 2021; **385:** 1833–44.
11 Fischer U, Kaesmacher J, Strbian D, et al. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. *Lancet* 2022; **400:** 104–15.
12 Mitchell PJ, Yan B, Churilov L, et al. Endovascular thrombectomy versus standard bridging thrombolytic with endovascular thrombectomy within 4·5 h of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. *Lancet* 2022; **400:** 116–25.
13 Nogueira RG, Tsivgoulis G. Large vessel occlusion strokes after the DIRECT-MT and SKIP trials: is the alteplase syringe half empty or half full? *Stroke* 2020; **51:** 3182–86.
14 Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischaemic stroke. *Stroke* 2013; **44:** 2650–63.
15 Goyal M, Fargen KM, Turk AS, et al. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. *J Neurointerv Surg* 2014; **6:** 83–86.
16 von Kummer R, Broderick JP, Campbell BCV, et al. The Heidelberg Bleeding Classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke* 2015; **46:** 2981–86.
17 MR CLEAN-NO IV. IRIS. https://mrclean-noiv.nl/iris.html (accessed July 28, 2023).
18 Saver JL, Mistry E. Time to recognize three classes of non-inferiority trial margins. *J Neurointerv Surg* 2023; **15:** 2–4.
19 Kaesmacher J, Mujanovic A, Treurniet K, et al. Perceived acceptable uncertainty regarding comparability of endovascular treatment alone versus intravenous thrombolysis plus endovascular treatment. *J Neurointerv Surg* 2023; **15:** 227–32.
20 Fisher DJ, Carpenter JR, Morris TP, Freeman SC, Tierney JF. Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach? *BMJ* 2017; **356:** j573.
21 Sera F, Armstrong B, Blangiardo M, Gasparrini A. An extended mixed-effects framework for meta-analysis. *Stat Med* 2019; **38:** 5429–44.
22 Schandelmaier S, Briel M, Varadhan R, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ* 2020; **192:** E901–06.
23 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* 2021; **10:** 89.
24 Fransen PSS, Berkhemer OA, Lingsma HF, et al. Time to reperfusion and treatment effect for acute ischemic stroke: a randomized clinical trial. *JAMA Neurol* 2016; **73:** 190–96.
25 Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014; **384:** 1929–35.
26 Katsanos AH, Malhotra K, Goyal N, et al. Intravenous thrombolysis prior to mechanical thrombectomy in large vessel occlusions. *Ann Neurol* 2019; **86:** 395–406.
27 Ye Z, Busse JW, Hill MD, et al. Endovascular thrombectomy and intravenous alteplase in patients with acute ischemic stroke due to large vessel occlusion: a clinical practice guideline. *J Evid Based Med* 2022; **15:** 263–71.
28 Fiehler J, Zeleňák K, Zapf A. The price of certainty: when is a new therapy good enough? *J Neurointerv Surg* 2021; **13:** 1065–66.
29 Mauri L, D'Agostino RBS Sr. Challenges in the design and interpretation of noninferiority trials. *N Engl J Med* 2017; **377:** 1357–67.
30 Brownlee S, Chalkidou K, Doust J, et al. Evidence for overuse of medical services around the world. *Lancet* 2017; **390:** 156–68.
31 Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; **39:** 119–77.
32 Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018; **378:** 1573–82.
33 Bala F, Singh N, Buck B, et al. Safety and efficacy of tenecteplase compared with alteplase in patients with large vessel occlusion stroke: a prespecified secondary analysis of the ACT randomised clinical trial. *JAMA Neurol* 2023; published online July 10. https://doi.org/10.1001/jamaneurol.2023.2094.