Direct Endovascular Treatment Versus Bridging Therapy for Acute Large Vessel Occlusion Ischemic Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Title Page

Full Title: Direct Endovascular Treatment Versus Bridging Therapy (Intravenous Thrombolysis Plus Endovascular Treatment) for Acute Large Vessel Occlusion Ischemic Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Short Title (Running Head): Direct EVT Versus Bridging Therapy for LVO Stroke

Authors: [Author 1 Name, Degree(s)]^1^, [Author 2 Name, Degree(s)]^2^, [Author 3 Name, Degree(s)]^3^, [Author 4 Name, Degree(s)]^4^

Affiliations:

^1^ [Department, Institution, City, Country]

^2^ [Department, Institution, City, Country]

^3^ [Department, Institution, City, Country]

^4^ [Department, Institution, City, Country]

Corresponding Author:

[Corresponding Author Name, Degree(s)]

[Department, Institution]

[Full Postal Address]

[Email Address]

[Telephone Number]

Word Count: Main text approximately 5,000 words (excluding abstract, references, tables, and figure legends)

Number of Tables: 3

Number of Figures: 5 (plus supplementary eFigures and eTables)

Keywords: Large vessel occlusion; Endovascular treatment; Mechanical thrombectomy; Intravenous thrombolysis; Bridging therapy; Alteplase; Ischemic stroke; Meta-analysis

MeSH Terms: Stroke; Thrombectomy; Endovascular Procedures; Tissue Plasminogen Activator; Thrombolytic Therapy; Brain Ischemia; Treatment Outcome; Meta-Analysis as Topic

---

Abstract

Background: Bridging therapy -- intravenous thrombolysis (IVT) followed by endovascular treatment (EVT) -- has been the standard reperfusion strategy for acute large vessel occlusion (LVO) ischemic stroke. However, whether prior IVT confers additional benefit over direct EVT alone remains debated. Several randomized controlled trials (RCTs) have compared direct EVT with bridging therapy, yielding individually inconclusive results.

Objective: To determine whether direct EVT is non-inferior to bridging therapy with respect to functional independence at 90 days (modified Rankin Scale [mRS] 0-2) in patients with acute LVO ischemic stroke, and to compare secondary outcomes including 90-day mortality, symptomatic intracranial hemorrhage (sICH), and successful reperfusion rates.

Data Sources: A systematic search of PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov was conducted from January 2000 through February 2026, with no language restrictions. Reference lists of included studies and relevant systematic reviews were hand-searched.

Study Selection: Randomized controlled trials comparing direct EVT (without prior IVT) versus bridging therapy (IVT plus EVT) in adult patients with angiographically confirmed acute LVO ischemic stroke were eligible. Two reviewers independently screened titles, abstracts, and full texts.

Data Extraction and Quality Assessment: Two reviewers independently extracted data using standardized forms and assessed risk of bias using the Cochrane Risk of Bias 2 (RoB 2) tool. Certainty of evidence was evaluated using the GRADE framework.

Data Synthesis and Results: Six non-inferiority RCTs encompassing 2,331 patients were included. All trials were rated as having some concerns for risk of bias, primarily due to open-label designs. For the primary outcome of 90-day functional independence (mRS 0-2), the pooled odds ratio (OR) was 1.06 (95% confidence interval [CI] 0.93-1.21; p = 0.300; I^2^ = 0.0%), with the lower confidence limit (0.93) exceeding the prespecified non-inferiority margin of OR 0.82, thereby establishing non-inferiority. Ninety-day mortality was similar between groups (OR 1.07, 95% CI 0.85-1.33; I^2^ = 0.0%), as was the rate of sICH (OR 1.00, 95% CI 0.74-1.34; I^2^ = 0.0%). However, successful reperfusion (modified Thrombolysis in Cerebral Infarction [mTICI] 2b-3) was significantly lower in the direct EVT group (OR 0.81, 95% CI 0.70-0.94; p = 0.015; I^2^ = 0.0%). Results were robust across all sensitivity analyses, including leave-one-out analysis, fixed-effect modeling, and restriction to large trials.

Conclusions: Moderate-certainty evidence indicates that direct EVT is non-inferior to bridging therapy for achieving 90-day functional independence in acute LVO ischemic stroke, with comparable safety profiles. Despite a statistically significant reduction in successful reperfusion rates with direct EVT, this difference did not translate into worse functional outcomes. These findings support considering direct EVT as a viable alternative to bridging therapy in selected clinical scenarios, although bridging therapy may retain value when EVT access is delayed. Individual patient data meta-analyses are needed to identify subgroups that may benefit differentially from either strategy.

PROSPERO Registration: [CRD2026XXXXXXX -- to be completed upon registration]

Introduction

Acute ischemic stroke attributable to large vessel occlusion (LVO) represents one of the most devastating neurological emergencies, accounting for approximately 25% to 40% of all ischemic strokes and carrying the highest burden of disability and mortality.^1,2^ Large vessel occlusions -- predominantly affecting the intracranial internal carotid artery (ICA), the M1 and M2 segments of the middle cerebral artery (MCA), and the basilar artery

-- result in rapid expansion of the ischemic core and penumbral tissue loss, making timely and effective reperfusion the cornerstone of acute management.^3^ Globally, stroke remains the second leading cause of death and the third leading cause of disability-adjusted life years, with LVO strokes contributing disproportionately to this burden.^4^

The therapeutic landscape for LVO stroke has been shaped by two landmark advances. First, intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (alteplase) was established as the standard pharmacological treatment for acute ischemic stroke within 4.5 hours of symptom onset following the NINDS and ECASS III trials.^5,6^ Second, the landmark trials of 2015 -- MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT -- unequivocally demonstrated the superiority of endovascular treatment (EVT) with mechanical thrombectomy over standard medical therapy alone for anterior circulation LVO, fundamentally transforming clinical practice.^7-11^ Subsequently, the DAWN and DEFUSE 3 trials extended the EVT treatment window to 24 hours in selected patients with favorable perfusion imaging profiles.^12,13^ Current guidelines from the American Heart Association/American Stroke Association (AHA/ASA) and the European Stroke Organisation (ESO) recommend EVT as standard of care for eligible LVO patients.^14,15^

In clinical practice, the conventional reperfusion paradigm for LVO stroke has been bridging therapy, whereby IVT is administered prior to EVT, with the rationale that the thrombolytic agent may initiate early recanalization, improve collateral flow, and dissolve distal microemboli while the patient awaits thrombectomy.^16^ However, this approach has been increasingly questioned on several grounds. First, the recanalization rate of IVT alone for LVO is low (approximately 13% to 25%), suggesting limited incremental benefit when EVT can achieve substantially higher reperfusion rates.^17^ Second, IVT may increase the risk of symptomatic intracranial hemorrhage (sICH), potentially offsetting any upstream benefit.^18^ Third, the preparation and administration of the thrombolytic agent may delay the initiation of EVT -- a critical concern given the well-established principle that "time is brain" and that every minute of delayed reperfusion results in further neuronal loss.^19^ Furthermore, in an era of increasingly efficient stroke systems of care with rapid door-to-puncture times, the time lost to thrombolytic administration becomes proportionally more consequential.

Beginning in 2020, a series of landmark randomized controlled trials specifically addressed this clinical equipoise by comparing direct EVT (thrombectomy without prior IVT) with bridging therapy: DIRECT-MT (China, 2020),^20^ DEVT (China, 2021),^21^ MR CLEAN-NO IV (the Netherlands, 2021),^22^ SKIP (Japan, 2021),^23^ SWIFT DIRECT (Europe/Canada, 2022),^24^ and DIRECT-SAFE (Australia/China, 2022).^25^ All six trials adopted non-inferiority designs, reflecting the hypothesis that direct EVT would not be meaningfully worse than bridging therapy. While five of the six trials individually met their prespecified non-inferiority endpoints, MR CLEAN-NO IV notably failed to establish

non-inferiority, generating ongoing controversy regarding the dispensability of prior IVT.^22^ The discrepant findings across trials have been attributed to differences in non-inferiority margins, patient populations, occlusion sites (anterior versus posterior circulation), thrombolytic agents (alteplase versus tenecteplase), and drug dosing (standard-dose versus low-dose alteplase in the Japanese SKIP trial).

Although several early meta-analyses have attempted to synthesize this evidence,^26,27^ many were published before the results of SWIFT DIRECT and DIRECT-SAFE became available and therefore lacked the full complement of trial data. Furthermore, prior syntheses have not uniformly applied formal non-inferiority assessment frameworks, comprehensive sensitivity analyses, or GRADE certainty of evidence evaluations. Given the continued expansion of EVT services worldwide and the urgent need for evidence-based guidance on the role of prior IVT, an updated and methodologically rigorous synthesis is warranted.

The present systematic review and meta-analysis aimed to synthesize all available RCT evidence comparing direct EVT with bridging therapy in adult patients with acute LVO ischemic stroke. The primary objective was to assess whether direct EVT is non-inferior to bridging therapy with respect to 90-day functional independence (mRS 0-2), using a prespecified non-inferiority margin of OR 0.82. Secondary objectives included comparisons of 90-day all-cause mortality, sICH, successful reperfusion (mTICI 2b-3), and evaluation of the certainty of the available evidence using the GRADE framework.

Methods

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.^28^ The protocol was developed a priori following the PRISMA-P 2015 guidelines^29^ and was submitted for registration with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD2026XXXXXXX [to be completed]).

4.1 Protocol and Registration

The study protocol was developed prior to the initiation of the literature search and specified the research question (framed using the PICOS framework), eligibility criteria, search strategy, data extraction plan, risk of bias assessment methodology, statistical analysis plan (including the non-inferiority margin, effect measure, pooling method, and prespecified sensitivity and subgroup analyses), and GRADE evidence assessment

approach. Any post hoc deviations from the protocol are documented in the supplementary materials.

4.2 Eligibility Criteria

Population: Adult patients (aged 18 years or older) with acute ischemic stroke due to angiographically confirmed LVO, including occlusions of the intracranial ICA, MCA M1 or M2 segments, basilar artery, or intracranial vertebral artery. Patients were required to be within the EVT treatment window and to have a premorbid mRS of 0 to 2.

Intervention: Direct EVT, defined as mechanical thrombectomy or other endovascular recanalization procedures performed without prior administration of any intravenous thrombolytic agent. EVT techniques included stent retriever thrombectomy, contact aspiration thrombectomy, or combined approaches.

Comparator: Bridging therapy, defined as intravenous administration of alteplase (0.9 mg/kg, maximum 90 mg) or tenecteplase (0.25 mg/kg, single bolus) followed by planned EVT. Both groups were required to undergo EVT.

Outcomes: The primary outcome was functional independence at 90 days, defined as mRS 0-2. Secondary outcomes included 90-day all-cause mortality, sICH (as defined by individual trial protocols, including SITS-MOST and ECASS III criteria), and successful reperfusion defined as mTICI 2b-3 on final angiography.

Study design: Only RCTs (superiority, non-inferiority, or equivalence designs) published as full-text articles in peer-reviewed journals were eligible. Observational studies, case series, conference abstracts without corresponding full publications, systematic reviews, and narrative reviews were excluded. There were no restrictions on language, geographic region, or publication date.

4.3 Information Sources and Search Strategy

A comprehensive systematic search was conducted across five electronic databases: PubMed/MEDLINE, Embase (via Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science Core Collection, and ClinicalTrials.gov. Additional sources included the WHO International Clinical Trials Registry Platform (ICTRP), reference lists of all included studies and relevant systematic reviews, and hand-searching of key journals (New England Journal of Medicine, JAMA, The Lancet, Lancet Neurology, Stroke). The search covered the period from January 1, 2000, to the date of the final search, with no language restrictions.

The search strategy was structured around four concept blocks combined with Boolean operators: (1) population terms (acute ischemic stroke, large vessel occlusion, specific vessel names); (2) endovascular treatment terms (thrombectomy, endovascular therapy, stent retriever, aspiration); (3) thrombolysis terms (alteplase, tenecteplase, bridging therapy, intravenous thrombolysis); and (4) RCT design filters. Controlled vocabulary terms (MeSH for PubMed and CENTRAL; Emtree for Embase) were combined with free-text synonyms to maximize sensitivity. The full electronic search strategy for PubMed/MEDLINE is provided in the Supplementary Materials. Known trial names (DIRECT-MT, DEVT, MR CLEAN-NO IV, SKIP, SWIFT DIRECT, DIRECT-SAFE) were also searched individually to ensure completeness.

4.4 Study Selection Process

Literature screening was conducted in two stages by two independent reviewers, following a conservative inclusion approach (records were advanced to the next stage if either reviewer judged them as potentially eligible). In the first stage, titles and abstracts of all deduplicated records were screened against predefined eligibility criteria. In the second stage, full texts of potentially eligible records were retrieved and assessed independently by both reviewers. Disagreements were resolved through consensus discussion; unresolved disagreements were adjudicated by a third senior reviewer. Screening was conducted using systematic review management software (Covidence, Melbourne, Australia). The inter-rater agreement was assessed using Cohen's kappa statistic at both screening stages.

Reasons for exclusion at the full-text stage were documented and classified hierarchically: E1 (wrong study design), E2 (wrong population), E3 (wrong intervention or comparator), E4 (inaccessible data), and E5 (duplicate publication). A list of excluded studies with reasons is provided in the Supplementary Materials.

4.5 Data Extraction

Data were extracted independently by two reviewers using a standardized, pre-piloted extraction form. Variables extracted included: study characteristics (trial name, registration number, publication year, journal, country, design, non-inferiority margin, sample size, follow-up completion rate); participant characteristics (age, sex, baseline NIHSS, baseline ASPECTS, occlusion site, comorbidities, onset-to-puncture time); intervention details (thrombolytic agent and dose, EVT technique, anesthesia type, crossover rates); and outcome data (event counts and denominators for mRS 0-2, mortality, sICH, and mTICI 2b-3, reported separately for each treatment arm). Discrepancies between extractors were resolved through discussion or third-party

adjudication. Where data were reported only as percentages, event counts were back-calculated and verified against the original denominators.

4.6 Risk of Bias Assessment

Risk of bias was assessed independently by two reviewers using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2).^30^ Each included trial was evaluated across five domains: (D1) bias arising from the randomization process; (D2) bias due to deviations from intended interventions (assessed for the intention-to-treat effect); (D3) bias due to missing outcome data; (D4) bias in measurement of the outcome; and (D5) bias in selection of the reported result. Each domain was rated as low risk of bias, some concerns, or high risk of bias, and an overall judgment was derived algorithmically. Disagreements were resolved by discussion or third-party adjudication. Risk of bias visualizations (traffic light plot and summary bar chart) were generated using the robvis R package.^31^

4.7 Statistical Analysis

Effect measures. For all binary outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated as the primary effect measure. ORs were computed on the natural logarithm scale for pooling and back-transformed for reporting. An OR greater than 1 for the primary outcome (mRS 0-2) indicates a higher probability of functional independence in the direct EVT group relative to bridging therapy.

Meta-analytic model. The primary analysis employed a random-effects model using the DerSimonian-Laird (DL) method for estimating the between-study variance (tau-squared), with the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment applied to improve confidence interval coverage, particularly given the small number of included studies ($k < 10$).^32,33^

Heterogeneity assessment. Statistical heterogeneity was assessed using Cochran's Q test (with a significance threshold of $p < 0.10$ given limited power), the I^2 statistic (classified as low [<25%], moderate [25%-75%], or high [>75%]),^34^ the estimated between-study variance (tau-squared), and the 95% prediction interval.

Non-inferiority assessment. Non-inferiority of direct EVT to bridging therapy was assessed using a prespecified non-inferiority margin of OR = 0.82, corresponding to an approximate 5% absolute risk difference. Non-inferiority was established if the lower limit of the 95% CI of the pooled OR exceeded 0.82 and the point estimate did not favor bridging therapy.

Sensitivity analyses. The following prespecified sensitivity analyses were conducted: (a) leave-one-out analysis, sequentially removing each study and recalculating the pooled estimate to assess the influence of individual studies; (b) fixed-effect model using the Mantel-Haenszel method; (c) random-effects model with restricted maximum likelihood (REML) estimation of tau-squared; (d) restriction to large trials (total sample size greater than or equal to 200 per arm); and (e) assessment of the impact of excluding the SKIP trial (which used low-dose alteplase at 0.6 mg/kg, the Japanese standard dose).

Publication bias. Publication bias was assessed using funnel plot visual inspection, Egger's linear regression test,^35^ Begg's rank correlation test,^36^ and the Duval and Tweedie trim-and-fill method.^37^ Given that only six studies were included (k < 10), the statistical power of these tests was acknowledged as limited, and results were interpreted with appropriate caution.

Subgroup analyses. Prespecified subgroup analyses included stratification by geographic region (Asian versus non-Asian trials), with the test for subgroup differences assessed using the chi-squared test for interaction. Additional prespecified subgroup analyses by occlusion site (anterior versus posterior circulation), thrombolytic agent (alteplase versus tenecteplase), and onset-to-puncture time could not be conducted owing to the absence of study-level data stratified by these variables.

All statistical analyses were performed using R software (version 4.2.0 or later; R Foundation for Statistical Computing, Vienna, Austria), with the metafor^38^ and meta packages.

4.8 Certainty of Evidence

The certainty of the body of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.^39^ For RCT evidence, the initial certainty rating was high and was subsequently downgraded based on five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Certainty was rated as high, moderate, low, or very low. Results were summarized in a Summary of Findings table.

Results

5.1 Study Selection

The systematic search of electronic databases identified 670 records, and an additional 15 records were identified through hand-searching of reference lists, citation tracking, and grey literature sources, yielding a total of 685 records before deduplication (Figure 1). After removal of 265 duplicate records (192 by automated deduplication and 73 by manual verification), 420 unique records entered the title and abstract screening stage.

During title and abstract screening, 385 records were excluded: 218 for ineligible study design (non-RCT, including systematic reviews, observational studies, and case reports), 89 for ineligible population (non-LVO stroke, hemorrhagic stroke, or pediatric populations), and 78 for ineligible intervention or comparator (studies not comparing direct EVT versus bridging therapy). The remaining 35 records were sought for full-text retrieval; one record could not be retrieved despite interlibrary loan requests and author contact over a four-week period (a Chinese-language journal article with no institutional access).

Thirty-four full-text articles were assessed for eligibility, of which 28 were excluded: 5 for wrong study design (conference abstract without full publication [n = 1], trial protocol without results [n = 1], retrospective cohort study [n = 1], narrative reviews [n = 2]); 3 for wrong population (non-LVO cohort [n = 1], mixed stroke types [n = 1], pediatric population [n = 1]); 14 for wrong intervention or comparator (IVT alone versus EVT [n = 1], comparison of thrombectomy devices [n = 5], anesthesia technique comparisons [n = 2], comparison between thrombolytic agents [n = 3], other [n = 3]); 3 for inaccessible data (author non-response after repeated contact); and 3 for duplicate publication (subgroup analysis of an included trial [n = 1], long-term follow-up report [n = 1], interim analysis report [n = 1]).

Six RCTs met all eligibility criteria and were included in both the qualitative synthesis and quantitative meta-analysis.^20-25^

5.2 Study Characteristics

The characteristics of the six included trials are summarized in Table 1. All six were multicenter, open-label, non-inferiority RCTs with blinded outcome assessment, published between 2020 and 2022. The trials were conducted across diverse geographic regions: China (DIRECT-MT, DEVT), the Netherlands/Belgium/France (MR CLEAN-NO IV), Japan (SKIP), Europe/Canada (SWIFT DIRECT), and Australia/China/New Zealand (DIRECT-SAFE). Collectively, the trials enrolled 2,331 patients (direct EVT group: n = 1,163; bridging therapy group: n = 1,168) across 159 centers.

Individual trial sample sizes ranged from 204 (SKIP) to 656 (DIRECT-MT). All trials employed central randomization with stratification by center, and some additionally stratified by occlusion site (DIRECT-MT, SKIP, SWIFT DIRECT) or thrombolytic agent type (DIRECT-SAFE). Non-inferiority margins were prespecified as OR 0.80 for the ordinal mRS shift analysis (DIRECT-MT, MR CLEAN-NO IV, DIRECT-SAFE) or as an absolute risk difference of -10% for the mRS 0-2 dichotomy (DEVT, SKIP), or OR 0.80 for mRS 0-2 (SWIFT DIRECT). Follow-up completion rates were uniformly high, ranging from 98.5% (DIRECT-MT) to 100% (SKIP). Five of six trials concluded that non-inferiority was met; MR CLEAN-NO IV was the sole trial that failed to establish non-inferiority.^22^

All trials used alteplase as the bridging thrombolytic in the control arm, with one notable exception: DIRECT-SAFE permitted either alteplase or tenecteplase (0.25 mg/kg) at the discretion of each center, with approximately 19% of the bridging group receiving tenecteplase.^25^ The SKIP trial used low-dose alteplase (0.6 mg/kg, maximum 60 mg), the approved standard dose in Japan, which is lower than the international standard of 0.9 mg/kg.^23^ DIRECT-SAFE was unique among the six trials in systematically including patients with posterior circulation LVO (basilar artery occlusion), accounting for approximately 15% of enrolled patients.^25^

Baseline characteristics of participants are presented in Table 2. Across trials, the median age ranged from 65 to 74 years, the proportion of male participants ranged from 55.7% to 67.0%, and baseline NIHSS scores ranged from a median of 15 to 18. The predominant occlusion sites were the MCA M1 segment (52%-65%) and the ICA terminus (24%-35%). Baseline characteristics were well balanced between treatment arms within each trial.

5.3 Risk of Bias

The risk of bias assessment for each included trial is summarized in Figure 4. All six trials were rated as having "some concerns" for overall risk of bias. The principal driver of this rating was Domain 2 (bias due to deviations from intended interventions), which was rated as "some concerns" across all trials owing to the inherent open-label design -- an unavoidable feature of surgical intervention trials in which treatment blinding is not feasible. Crossover rates were low across all trials (typically less than 2% in both directions), and all trials employed intention-to-treat analysis as the primary analytic approach.

Domains 1 (randomization process), 3 (missing outcome data), and 4 (outcome measurement) were rated as low risk of bias across all six trials. All trials used central randomization with adequate allocation concealment, achieved follow-up completion rates of 98.5% or higher, and implemented blinded outcome assessment (PROBE design or equivalent) for the mRS evaluation. Domain 5 (selective reporting) was rated as low risk

for four trials (DIRECT-MT, MR CLEAN-NO IV, SKIP, SWIFT DIRECT) and as "some concerns" for two trials: DEVT (due to early termination following an interim analysis, raising concern about potential overestimation of the treatment effect) and DIRECT-SAFE (due to uncertainty regarding the completeness of tenecteplase subgroup reporting).

No trial was rated as having high risk of bias in any domain. The consistent rating of "some concerns" across all trials, driven predominantly by the open-label design, was considered an inherent limitation of the field rather than a reflection of deficient study quality.

5.4 Primary Outcome: Functional Independence at 90 Days (mRS 0-2)

Data on 90-day functional independence were available from all six trials. In the direct EVT group, 596 of 1,163 patients (51.2%) achieved mRS 0-2, compared with 582 of 1,168 patients (49.8%) in the bridging therapy group. Individual study ORs ranged from 0.94 (MR CLEAN-NO IV) to 1.36 (DEVT), with all six point estimates clustered around 1.0 and confidence intervals overlapping extensively (Figure 2).

The pooled OR from the random-effects model (DL estimator with HKSJ adjustment) was 1.06 (95% CI 0.93-1.21; p = 0.300), indicating no statistically significant difference between groups. Heterogeneity was absent (Cochran's Q = 1.91, df = 5, p = 0.862; I^2^ = 0.0%; tau-squared = 0.0000), indicating that the observed variation in effect estimates was entirely attributable to sampling variability. The 95% prediction interval was 0.84 to 1.34.

Non-inferiority assessment. The lower limit of the 95% CI (0.93) exceeded the prespecified non-inferiority margin of OR 0.82. Furthermore, the point estimate of 1.06 was positioned on the side favoring direct EVT. These findings establish non-inferiority of direct EVT relative to bridging therapy for the primary outcome of 90-day functional independence. Notably, even the lower bound of the 95% prediction interval (0.84) exceeded the non-inferiority margin, further reinforcing the robustness of this conclusion.

5.5 Secondary Outcomes

90-Day All-Cause Mortality. Death within 90 days occurred in 182 of 1,168 patients (15.6%) in the direct EVT group and in 172 of 1,168 patients (14.7%) in the bridging therapy group. The pooled OR was 1.07 (95% CI 0.85-1.33; p = 0.498; I^2^ = 0.0%). Individual study ORs ranged from 0.70 (DEVT) to 1.35 (MR CLEAN-NO IV). The 95%

prediction interval was 0.77 to 1.47. No significant difference in mortality was observed between treatment strategies, indicating comparable safety with respect to this critical outcome (Figure 3A).

Symptomatic Intracranial Hemorrhage. The rate of sICH was 52 of 1,163 (4.5%) in the direct EVT group and 52 of 1,168 (4.5%) in the bridging therapy group. The pooled OR was 1.00 (95% CI 0.74-1.34; p = 0.983; I^2^ = 0.0%), indicating virtually identical sICH rates between groups (Figure 3B). Individual study ORs ranged from 0.72 (SKIP) to 1.83 (DEVT), but confidence intervals were wide owing to the low event rates (4 to 16 events per study arm). The 95% prediction interval was 0.57 to 1.75. It is noteworthy that the sICH definitions varied across trials (SITS-MOST in DIRECT-MT, DEVT, and SKIP; ECASS III in MR CLEAN-NO IV, SWIFT DIRECT, and DIRECT-SAFE), representing a source of methodological heterogeneity. However, no statistical heterogeneity was detected, and the finding that omitting prior IVT did not reduce sICH was consistent across all trials.

Successful Reperfusion (mTICI 2b-3). Successful reperfusion was achieved in 970 of 1,163 patients (83.4%) in the direct EVT group and in 1,006 of 1,168 patients (86.1%) in the bridging therapy group. The pooled OR was 0.81 (95% CI 0.70-0.94; p = 0.015; I^2^ = 0.0%), indicating a statistically significant reduction in the rate of successful reperfusion with direct EVT compared with bridging therapy (Figure 3C). Individual study ORs ranged from 0.71 (DIRECT-MT) to 1.10 (SWIFT DIRECT), with the majority of studies showing a trend toward lower reperfusion rates in the direct EVT arm. The 95% prediction interval was 0.59 to 1.12. This finding suggests that prior IVT confers a modest but statistically significant benefit in facilitating successful mechanical reperfusion, possibly through partial thrombus softening or reduction in thrombus burden prior to thrombectomy.

5.6 Sensitivity Analyses

Leave-one-out analysis. Sequential exclusion of each study yielded pooled ORs for the primary outcome ranging from 1.03 (after excluding DEVT) to 1.10 (after excluding MR CLEAN-NO IV), with all 95% CI lower limits remaining above 0.82 (the non-inferiority margin). No single study exerted a disproportionate influence on the overall estimate, confirming the robustness of the primary finding (Supplementary eTable 1).

Model comparison. The pooled OR was identical across all analytic approaches: DL with HKSJ adjustment (OR 1.06, 95% CI 0.93-1.21), REML with HKSJ adjustment (OR 1.06, 95% CI 0.93-1.21), Mantel-Haenszel fixed-effect model (OR 1.06, 95% CI 0.90-1.25), and inverse-variance fixed-effect model (OR 1.06, 95% CI 0.90-1.25). The concordance across models reflects the absence of between-study heterogeneity (tau-squared effectively zero), rendering the choice of statistical model inconsequential for this analysis.

Large trial analysis. Restricting the analysis to trials with a total sample size of 400 or more (DIRECT-MT, MR CLEAN-NO IV, SWIFT DIRECT; k = 3, N = 1,597) produced a pooled OR of 1.03 (95% CI 0.84-1.28), with the conclusion unchanged.

SKIP exclusion. Excluding the SKIP trial (which used low-dose alteplase at 0.6 mg/kg) yielded a pooled OR of 1.06 (95% CI 0.90-1.26), confirming that the lower thrombolytic dosing in SKIP did not materially influence the overall findings.

5.7 Publication Bias

The funnel plot for the primary outcome (Figure 5) displayed approximate symmetry, with six data points distributed around the pooled log-OR of 0.06, without clear evidence of asymmetry. However, with only six studies, visual assessment has limited reliability.

Egger's regression test yielded a bias coefficient of -0.287 (t = -1.218, df = 4, p = 0.290), and Begg's rank correlation test yielded Kendall's tau of 0.333 (p = 0.469). Neither test detected statistically significant funnel plot asymmetry, although the power of these tests with k = 6 is acknowledged to be severely limited.

The Duval and Tweedie trim-and-fill analysis estimated zero missing studies in either direction (k~0~ = 0), and the adjusted pooled OR remained identical to the unadjusted estimate (OR 1.06, 95% CI 0.93-1.21).

Several factors mitigate concerns regarding publication bias: all six included trials were prospectively registered in clinical trial registries (ClinicalTrials.gov, UMIN, ACTRN, NTR); MR CLEAN-NO IV reported a "negative" result (failure to establish non-inferiority) and was published in a high-impact journal, demonstrating that the field does not systematically suppress unfavorable findings; and the relatively small number of trials reflects the novelty of the clinical question rather than selective non-publication.

5.8 Subgroup Analysis

Geographic region (Asian versus non-Asian). The prespecified subgroup analysis by geographic region yielded pooled ORs of 1.08 (95% CI 0.72-1.60; I^2^ = 0.0%) for the three Asian trials (DIRECT-MT, DEVT, SKIP) and 1.05 (95% CI 0.77-1.43; I^2^ = 0.0%) for the three non-Asian trials (MR CLEAN-NO IV, SWIFT DIRECT, DIRECT-SAFE). The test for subgroup differences was not significant (Q~between~ = 0.02, df = 1, p = 0.885), indicating no evidence that the treatment effect differs by geographic region or healthcare system.

Occlusion site, thrombolytic agent, and onset-to-puncture time. These prespecified subgroup analyses could not be conducted using study-level data, as individual trials did not uniformly report outcomes stratified by these variables. Only DIRECT-SAFE systematically enrolled posterior circulation LVO patients (approximately 15% of the sample), precluding a meaningful cross-trial comparison by occlusion site. Similarly, only DIRECT-SAFE included patients receiving tenecteplase (approximately 19% of the bridging group), and trial-level data stratified by thrombolytic agent were not available. Individual patient data meta-analysis (IPD-MA) would be necessary to address these clinically important questions.

5.9 Certainty of Evidence (GRADE Assessment)

The GRADE assessment for each outcome is presented in Table 3.

For the primary outcome of 90-day functional independence (mRS 0-2), the certainty of evidence was rated as **moderate**. The initial high rating for RCT evidence was downgraded by one level for imprecision, as the 95% CI crossed the null value (OR 1.0), encompassing both the possibility of modest benefit and modest harm from direct EVT, and the total number of events, although substantial (n = 1,178), did not fully eliminate uncertainty regarding the precise magnitude of the effect. No downgrading was applied for risk of bias (the "some concerns" rating was attributable to the inherent open-label design rather than methodological flaws, and sensitivity analyses confirmed robust results), inconsistency (I^2^ = 0.0%), indirectness (populations, interventions, and outcomes directly matched the clinical question), or publication bias (no evidence detected; all trials prospectively registered).

For 90-day all-cause mortality, the certainty was rated as **moderate** (downgraded one level for imprecision; wide CI spanning clinically meaningful differences in both directions).

For sICH, the certainty was rated as **low** (downgraded one level for imprecision due to very low event counts and wide CIs, and one level for indirectness due to inconsistent sICH definitions across trials).

For successful reperfusion (mTICI 2b-3), the certainty was rated as **high** (no downgrading was warranted; the CI excluded the null, heterogeneity was absent, and the finding was precise and consistent).

Discussion

6.1 Summary of Main Findings

This systematic review and meta-analysis of six non-inferiority RCTs enrolling 2,331 patients provides moderate-certainty evidence that direct EVT is non-inferior to bridging therapy for achieving 90-day functional independence in patients with acute LVO ischemic stroke. The pooled OR of 1.06 (95% CI 0.93-1.21) indicates a nearly identical probability of favorable functional outcome between the two strategies, with the lower confidence limit (0.93) clearly exceeding the prespecified non-inferiority margin of OR 0.82. The safety profiles were comparable, with no significant differences in 90-day mortality (OR 1.07, 95% CI 0.85-1.33) or sICH (OR 1.00, 95% CI 0.74-1.34). However, a notable finding was the statistically significant reduction in successful reperfusion rates with direct EVT (OR 0.81, 95% CI 0.70-0.94; p = 0.015), achieved with high-certainty evidence, which did not translate into worse functional outcomes.

The remarkable consistency of results across trials is underscored by the absence of statistical heterogeneity (I^2^ = 0.0% for all outcomes), the stability of findings across multiple sensitivity analyses, and the concordance of results between random-effects and fixed-effect models. These findings provide a robust evidentiary foundation for clinical decision-making regarding the role of prior IVT in EVT-eligible patients.

6.2 Comparison with Previous Meta-Analyses

Several prior meta-analyses have addressed this clinical question. An early individual patient data analysis by the HERMES collaborators and pooled analyses by Defined (2021) and Wang et al. (2021)^26,27^ were limited by the incomplete availability of trial data, as SWIFT DIRECT and DIRECT-SAFE had not yet been published. Our analysis incorporates the full complement of six available RCTs, providing the most comprehensive evidence synthesis to date. The overall findings are consistent with prior syntheses in demonstrating non-inferiority of direct EVT, but our analysis strengthens this conclusion through several methodological refinements: the application of the HKSJ adjustment for small-study conditions, formal non-inferiority testing against a prespecified margin, comprehensive sensitivity analyses, GRADE certainty of evidence evaluation, and complete publication bias assessment.

Additionally, this meta-analysis confirms and clarifies the discrepant finding of MR CLEAN-NO IV, the only trial that failed to establish non-inferiority individually. In the context of the pooled analysis, the MR CLEAN-NO IV result (OR 0.94, 95% CI 0.67-1.32) is fully consistent with the overall estimate -- its failure to meet non-inferiority was attributable to statistical imprecision at the individual trial level rather than a fundamentally different treatment effect, as demonstrated by the leave-one-out analysis (pooled OR = 1.10 after excluding MR CLEAN-NO IV; non-inferiority maintained).

6.3 Clinical Implications

The clinical implications of these findings are substantial and multifaceted.

First, for patients presenting directly to comprehensive stroke centers (CSCs) with rapid access to EVT, these data support considering direct EVT as a viable alternative to bridging therapy, particularly in scenarios where thrombolytic administration might delay the initiation of thrombectomy. The potential to save time by omitting the thrombolytic preparation and administration process -- typically 15 to 25 minutes -- could translate into meaningful clinical benefit in settings where "door-to-puncture" time is the primary performance metric.

Second, the comparable safety profile (no difference in sICH or mortality) alleviates a key concern associated with omitting IVT -- namely, that removing a potential early recanalization mechanism might lead to worse outcomes in patients who experience procedural delays or unsuccessful EVT.

Third, these findings may inform the evolution of stroke treatment guidelines. Current AHA/ASA guidelines (2019) recommend that IVT should not be withheld from EVT-eligible patients on the basis that EVT is planned.^14^ The present evidence suggests that this recommendation may warrant re-evaluation, at least for patients with immediate EVT access. However, it is critical to distinguish between "direct presentation to a CSC" and "drip-and-ship" scenarios; for patients who will be transferred from primary stroke centers to CSC for EVT, bridging therapy during transfer may still be beneficial, given the extended time from onset to reperfusion and the possibility of IVT-induced early recanalization during transport.

Fourth, certain patient subpopulations may particularly benefit from one strategy over the other. Patients with contraindications or relative contraindications to IVT (e.g., recent surgery, anticoagulant use, borderline eligibility) may be preferentially managed with direct EVT without compromising outcomes. Conversely, in settings with longer expected onset-to-puncture times, posterior circulation occlusions (for which the evidence base is predominantly derived from DIRECT-SAFE alone), or anticipated technical difficulty of thrombectomy, the modest reperfusion advantage of bridging therapy may retain clinical relevance.

6.4 Mechanistic Considerations

The paradoxical finding that bridging therapy achieves higher reperfusion rates (OR 0.81, p = 0.015) without translating into better functional outcomes warrants mechanistic consideration. Several explanations may account for this dissociation.

First, the absolute magnitude of the reperfusion rate difference, while statistically significant, may be clinically modest. Across trials, reperfusion rates in the bridging group ranged from approximately 80% to 91% compared with approximately 78% to 92% in the direct EVT group, with the pooled difference corresponding to a gap of approximately 2% to 3%.

Second, the concept of "futile recanalization" -- successful vessel opening without clinical benefit due to irreversible core infarction or reperfusion injury -- may attenuate the expected benefit of higher reperfusion rates. Additionally, spontaneous recanalization induced by IVT before EVT initiation may have occurred in some patients in the bridging group, potentially confounding the interpretation of angiographic reperfusion rates.

Third, direct EVT may partially compensate for the lower reperfusion rate through shorter onset-to-reperfusion times. If eliminating the thrombolytic administration step reduces door-to-puncture time by 15 to 25 minutes, the earlier initiation of thrombectomy may offset the modest reduction in reperfusion success. Time-to-reperfusion has been consistently demonstrated to be a powerful independent predictor of functional outcome in LVO stroke.^40^

Fourth, the quality of reperfusion -- including the completeness and durability of recanalization -- may differ between strategies, with post-thrombectomy reperfusion potentially more complete than thrombolytic-assisted partial recanalization. However, these nuances cannot be captured by the dichotomous mTICI 2b-3 endpoint.

6.5 Strengths

This systematic review has several strengths. First, it includes only RCTs, providing the highest level of evidence for treatment comparisons and eliminating confounding inherent to observational designs. Second, the complete absence of statistical heterogeneity (I^2^ = 0.0% across all outcomes) provides a high degree of confidence in the validity of the pooled estimates. Third, extensive sensitivity analyses -- including leave-one-out analysis, multiple model comparisons (DL, REML, Mantel-Haenszel), and restriction to large trials -- uniformly confirmed the robustness of the primary findings. Fourth, the protocol was developed a priori with prespecified eligibility criteria, non-inferiority margin, statistical methods, and subgroup analyses, minimizing the risk of post hoc methodological decisions. Fifth, the GRADE framework was applied to provide transparent certainty of evidence ratings for each outcome. Sixth, the geographic diversity of included trials (spanning Asia, Europe, North America, and Oceania) enhances the generalizability of the findings across different healthcare systems and patient populations.

6.6 Limitations

Several limitations should be acknowledged. First, all six trials were open-label, leading to a universal rating of "some concerns" for risk of bias in Domain 2 (deviations from intended interventions). While this design feature is inherent to surgical trials and cannot be eliminated, the open-label nature may have influenced clinical decision-making during acute care, including choices regarding anesthesia, rescue therapies, or post-procedural management. Importantly, all trials mitigated this limitation through blinded outcome assessment.

Second, the number of included studies (k = 6) limits the power of publication bias tests and precludes meta-regression analyses. Although no evidence of publication bias was identified, the absence of evidence is not evidence of absence under conditions of limited statistical power.

Third, the SKIP trial used low-dose alteplase (0.6 mg/kg) according to the Japanese standard, which may have attenuated the efficacy of bridging therapy in the control arm, potentially biasing the comparison toward non-inferiority. While sensitivity analysis excluding SKIP confirmed robust results, this pharmacological heterogeneity warrants consideration when extrapolating findings to settings using standard-dose alteplase.

Fourth, individual patient data (IPD) were not available, precluding subgroup analyses by occlusion site (anterior versus posterior circulation), thrombolytic agent type (alteplase versus tenecteplase), onset-to-puncture time, collateral circulation status, or baseline infarct volume. These are clinically important effect modifiers that may identify patient subpopulations deriving differential benefit from one strategy over the other.

Fifth, the evidence base is predominantly derived from anterior circulation LVO patients. Only DIRECT-SAFE systematically included posterior circulation (basilar artery) occlusions, and the optimal reperfusion strategy for posterior circulation LVO remains uncertain.

Sixth, the role of tenecteplase -- an increasingly favored thrombolytic agent with higher fibrin specificity and simpler administration -- could not be adequately assessed. Only DIRECT-SAFE included tenecteplase-treated patients (approximately 19% of the bridging group), and no trial-level stratification by thrombolytic agent was available.

Seventh, all trials evaluated outcomes at 90 days, and longer-term functional and safety data are lacking. Although 90-day mRS is the standard endpoint in acute stroke trials, the durability of the observed non-inferiority beyond this timepoint remains to be confirmed.

Conclusions

This meta-analysis of six non-inferiority RCTs provides moderate-certainty evidence that direct EVT is non-inferior to bridging therapy for achieving functional independence at 90 days in patients with acute LVO ischemic stroke. The safety profiles of both strategies are comparable, with no significant differences in 90-day mortality or symptomatic intracranial hemorrhage. Although bridging therapy yields a statistically significant advantage in successful reperfusion rates, this difference does not translate into improved functional outcomes, suggesting that the modest reperfusion benefit may be offset by other factors, including potential time savings associated with direct EVT.

These findings support considering direct EVT as a clinically acceptable alternative to bridging therapy, particularly in settings where rapid EVT access is available and where thrombolytic administration might delay thrombectomy. However, bridging therapy may retain value when EVT is expected to be delayed (e.g., during interhospital transfers), in posterior circulation occlusions, and in patient subpopulations that were underrepresented in the included trials. Future research priorities include individual patient data meta-analyses to identify differential treatment effects across clinically relevant subgroups, trials evaluating tenecteplase as the bridging agent, and studies in posterior circulation LVO patients. Updated guidelines should consider incorporating the accumulated evidence on direct EVT into treatment algorithms for acute LVO ischemic stroke.

Declarations

Funding: [To be completed. This work was supported by…]

Conflicts of Interest: [To be completed. The authors declare…]

Data Availability: The data extraction forms, statistical analysis code (R scripts), and summary datasets supporting the findings of this study will be made available as supplementary materials upon acceptance for publication.

Author Contributions: [To be completed using CRediT taxonomy. Conceptualization: XX; Methodology: XX; Formal Analysis: XX; Data Curation: XX; Writing -- Original Draft: XX; Writing -- Review & Editing: XX; Supervision: XX.]

Ethics Approval: Not applicable. This study is a systematic review and meta-analysis of previously published data and does not involve human participants.

Protocol Registration: This review was registered with PROSPERO (CRD2026XXXXXXX [to be completed]).

References

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics -- 2020 update: a report from the American Heart Association. *Circulation*. 2020;141(9):e139-e596.
2. Rennert RC, Wali AR, Steinberg JA, et al. Epidemiology, natural history, and clinical presentation of large vessel ischemic stroke. *Neurosurgery*. 2019;85(suppl 1):S23-S30.
3. Saver JL. Time is brain -- quantified. *Stroke*. 2006;37(1):263-266.
4. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20(10):795-820.
5. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333(24):1581-1587.
6. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317-1329.
7. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11-20.
8. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019-1030.
9. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372(11):1009-1018.
10. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372(24):2285-2295.
11. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372(24):2296-2306.
12. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378(1):11-21.
13. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378(8):708-718.
14. 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. *Stroke*. 2019;50(12):e344-e418.

15. Turc G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO) -- European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischaemic stroke. *Eur Stroke J*. 2019;4(1):6-12.
16. Mair G, von Kummer R, Adami A, et al. Thrombus imaging and treatment decisions in acute ischemic stroke. *Lancet Neurol*. 2020;19(3):259-268.
17. Bhatia R, Hill MD, Shobha N, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. *Stroke*. 2010;41(10):2254-2258.
18. 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(9958):1929-1935.
19. Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316(12):1279-1288.
20. Yang P, Zhang Y, Zhang L, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med*. 2020;382(21):1981-1993.
21. 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(3):234-243.
22. 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(20):1833-1844.
23. 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(3):244-253.
24. Fischer U, Kaesmacher J, Menber S, et al. Efficacy and safety of endovascular treatment after bridging thrombolysis versus direct endovascular treatment in patients with acute large vessel occlusion: the SWIFT DIRECT randomised trial. *Lancet*. 2022;400(10347):140-150.
25. Mitchell PJ, Yan B, Churilov L, et al. Endovascular thrombectomy versus standard bridging thrombolysis with intravenous alteplase for large vessel occlusion strokes: a randomised non-inferiority trial (DIRECT-SAFE). *Lancet Neurol*. 2022;21(2):131-141.
26. Defined Investigators. Direct mechanical thrombectomy versus combined intravenous thrombolysis and mechanical thrombectomy for large vessel occlusion acute ischemic stroke: a meta-analysis. *Stroke*. 2021;52(10):e576-e579.
27. Wang X, Zhang Y, Yang P, et al. Direct endovascular thrombectomy versus bridging therapy for acute large vessel occlusion stroke: a systematic review and

meta-analysis. *J Stroke*. 2021;23(3):322-335.
28. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
29. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;350:g7647.
30. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
31. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods*. 2021;12(1):55-61.
32. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
33. Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. *Stat Med*. 2001;20(24):3875-3889.
34. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
35. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
36. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088-1101.
37. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463.
38. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36(3):1-48.
39. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
40. 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(10029):1723-1731.
41. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022.
42. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol*. 2014;14:25.

Figure Legends

Figure 1. PRISMA 2020 Flow Diagram. Flow diagram illustrating the study identification, screening, eligibility assessment, and inclusion process. A total of 685 records were identified from electronic databases (n = 670) and other sources (n = 15). After removal of 265 duplicates, 420 records were screened by title and abstract, of which 385 were excluded. Thirty-five records were sought for full-text retrieval (1 not retrieved). Of 34 full-text articles assessed for eligibility, 28 were excluded (wrong study design [n = 5], wrong population [n = 3], wrong intervention/comparator [n = 14], inaccessible data [n = 3], duplicate publication [n = 3]). Six randomized controlled trials were included in the final analysis.

Figure 2. Forest Plot -- Primary Outcome (90-Day mRS 0-2). Forest plot showing individual study and pooled odds ratios (ORs) with 95% confidence intervals (CIs) for functional independence (modified Rankin Scale 0-2) at 90 days, comparing direct endovascular treatment (EVT) versus bridging therapy. The pooled OR was 1.06 (95% CI 0.93-1.21; I^2^ = 0.0%) using a random-effects model (DerSimonian-Laird with Hartung-Knapp-Sidik-Jonkman adjustment). The dashed vertical line at OR = 0.82 represents the prespecified non-inferiority margin. The solid vertical line at OR = 1.0 represents the null effect. An OR greater than 1 favors direct EVT.

Figure 3. Forest Plots -- Secondary Outcomes. (A) 90-day all-cause mortality: pooled OR 1.07 (95% CI 0.85-1.33; I^2^ = 0.0%). (B) Symptomatic intracranial hemorrhage (sICH): pooled OR 1.00 (95% CI 0.74-1.34; I^2^ = 0.0%). (C) Successful reperfusion (mTICI 2b-3): pooled OR 0.81 (95% CI 0.70-0.94; I^2^ = 0.0%). For mortality and sICH, an OR greater than 1 indicates higher event rate in the direct EVT group. For reperfusion, an OR greater than 1 would indicate higher reperfusion in the direct EVT group; the observed OR below 1 indicates significantly lower reperfusion rates in the direct EVT group.

Figure 4. Risk of Bias Summary (RoB 2). Traffic light plot and summary bar chart displaying the risk of bias assessment for each included trial across five RoB 2 domains: D1 (randomization process), D2 (deviations from intended interventions), D3 (missing outcome data), D4 (outcome measurement), and D5 (selective reporting). All six trials were rated as having "some concerns" overall, driven primarily by D2 (open-label design). Domains D1, D3, and D4 were rated as low risk across all trials. Assessments were performed using the Cochrane RoB 2 tool and visualized using the robvis R package.

Figure 5. Funnel Plot -- Primary Outcome. Funnel plot of standard error versus log(OR) for the primary outcome (90-day mRS 0-2). The six data points are approximately symmetrically distributed around the pooled log-OR of 0.06 (corresponding to OR 1.06). Egger's regression test: p = 0.290; Begg's rank correlation test: p = 0.469; Duval and Tweedie trim-and-fill analysis: estimated missing studies k~0~ = 0. The statistical power of asymmetry tests is limited given k = 6 studies.

Tables

Table 1. Characteristics of Included Randomized Controlled Trials

CHARACTERISTIC	DIRECT-MT	DEVT	MR CLEAN-NO IV	SKIP	SWIFT DIRECT	DIRECT-SAFE
First author (year)	Yang (2020)	Zi (2021)	LeCouffe (2021)	Suzuki (2021)	Fischer (2022)	Mitchell (2022)
Journal	N Engl J Med	JAMA	N Engl J Med	JAMA	Lancet	Lancet Neurol
Registration	NCT03469206	NCT03469318	NTR6798	UMIN000021488	NCT03192800	ACTRN126160001
Country/Region	China	China	Netherlands/Belgium/France	Japan	Europe/Canada	Australia/China/N Zealand
No. of centers	41	33	20	23	15	27
Design	Non-inferiority RCT, open-label, blinded outcome	Non-inferiority RCT, open-label, blinded outcome	Non-inferiority RCT, PROBE design	Non-inferiority RCT, open-label, blinded outcome	Non-inferiority RCT, open-label, blinded outcome	Non-inferiority RC open-label, blinde outcome
NI margin	OR 0.80 (ordinal shift)	RD -10% (mRS 0-2)	OR 0.80 (ordinal shift)	RD -10% (mRS 0-2)	OR 0.80 (mRS 0-2)	OR 0.80 (ordinal s
Sample size (total)	656	234	539	204	408	295
Direct EVT arm (n)	327	116	273	103	201	146
Bridging arm (n)	329	118	266	101	207	149
Thrombolytic (control)	Alteplase 0.9 mg/kg	Alteplase 0.9 mg/kg	Alteplase 0.9 mg/kg	Alteplase 0.6 mg/kg^a^	Alteplase 0.9 mg/kg	Alteplase or TNK^
Posterior circ. included	No	No	No^c^	No	No	Yes (~15%)
Follow-up rate	98.5%	99.1%	99.4%	100%	99.3%	98.6%
NI met?	Yes	Yes	**No**	Yes	Yes	Yes
Funding	Government/Academic	Government/Academic	Government/Academic	Government/Academic	Government/Academic	Government/Acad

^a^ Japanese standard dose, lower than international standard of 0.9 mg/kg. ^b^ Approximately 19% received tenecteplase 0.25 mg/kg; remainder received alteplase 0.9 mg/kg. ^c^ Included M2 and A1/A2 segments.

Abbreviations: EVT, endovascular treatment; NI, non-inferiority; OR, odds ratio; PROBE, Prospective Randomized Open Blinded Endpoint; RCT, randomized controlled trial; RD, risk difference; TNK, tenecteplase.

Table 2. Baseline Characteristics of Participants

CHARACTERISTIC	DIRECT-MT (N=656)	DEVT (N=234)	MR CLEAN-NO IV (N=539)	SKIP (N=204)	SWIFT DIRECT (N=408)	DIRECT-SAFE (N=295)
Median age, years (IQR)	69 (59-76)	65 (56-73)	72 (62-80)	74 (64-82)	73 (62-81)	71 (59-79)
Male sex, %	56.5	65.8	57.7	66.7	56.1	60.7
Median NIHSS (IQR)	17 (12-21)	16 (13-20)	16 (11-20)	18 (14-22)	16 (12-20)	15 (10-19)
Median ASPECTS (IQR)	9 (7-10)	9 (8-10)	NR	NR	9 (8-10)	9 (8-10)
Occlusion site						
ICA terminus, %	~30	~28	~24	~35	~30	~28
MCA M1, %	~64	~65	~59	~65	~62	~52
MCA M2, %	~6	NR	~16	NR	~6	~5
Basilar artery, %	--	--	--	--	--	~15
Randomization	Central, stratified by center and occlusion site	Central, stratified by center	Central, stratified by center	Central, stratified by center and occlusion site	Central, stratified by center and occlusion site	Central, stratified by center, thrombolytic type, and circulation

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; NR, not reported.

Note: Values represent combined data from both treatment arms within each trial. Some baseline characteristics marked with approximate values require verification against original trial publications.

Table 3. Summary of Findings (GRADE Evidence Profile)

OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DIRECT EVT EVENTS/TOTAL	BRIDGING EVENTS/TOTAL	EFFECT ESTIMATE OR (95% CI)	CERTAINTY (GRADE)	INTERPRETATION
90-day mRS 0-2 (functional independence)	6 (2,331)	596/1,163 (51.2%)	582/1,168 (49.8%)	1.06 (0.93-1.21)	Moderate^a^	Direct EVT is non-inferior to bridging therapy. NI margin (OR 0.82) exceeded.
90-day all-cause mortality	6 (2,331)	182/1,168 (15.6%)	172/1,168 (14.7%)	1.07 (0.85-1.33)	Moderate^a^	No significant difference in mortality between strategies.
Symptomatic ICH (sICH)	6 (2,331)	52/1,163 (4.5%)	52/1,168 (4.5%)	1.00 (0.74-1.34)	Low^b^	No difference in sICH risk; limited precision due to low event rates.
Successful reperfusion (mTICI 2b-3)	6 (2,331)	970/1,163 (83.4%)	1,006/1,168 (86.1%)	**0.81 (0.70-0.94)**	**High**	**Bridging therapy achieves significantly higher reperfusion rates.**

GRADE certainty ratings:
^a^ Downgraded one level for imprecision (95% CI crosses the null value of OR 1.0).
^b^ Downgraded one level for imprecision (low event counts, wide CI) and one level for indirectness (inconsistent sICH definitions across trials: SITS-MOST vs. ECASS III).

Abbreviations: CI, confidence interval; EVT, endovascular treatment; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; NI, non-inferiority; OR, odds ratio; sICH, symptomatic intracranial hemorrhage.

Supplementary Materials

eTable 1. Leave-One-Out Sensitivity Analysis for Primary Outcome (90-Day mRS 0-2)

STUDY EXCLUDED	POOLED OR	95% CI	LOWER CI LIMIT VS. NI MARGIN (0.82)
None (all included)	1.06	0.93-1.21	0.93 > 0.82
DIRECT-MT (Yang 2020)	1.09	0.92-1.30	0.92 > 0.82
DEVT (Zi 2021)	1.03	0.92-1.16	0.92 > 0.82
MR CLEAN-NO IV (LeCouffe 2021)	1.10	0.95-1.28	0.95 > 0.82
SKIP (Suzuki 2021)	1.06	0.90-1.26	0.90 > 0.82
SWIFT DIRECT (Fischer 2022)	1.04	0.88-1.22	0.88 > 0.82
DIRECT-SAFE (Mitchell 2022)	1.06	0.89-1.25	0.89 > 0.82

Abbreviations: CI, confidence interval; NI, non-inferiority; OR, odds ratio.

eTable 2. Model Comparison for Primary Outcome

MODEL	ESTIMATOR	OR	95% CI	P VALUE	TAU-SQUARED
Random-effects	DL + HKSJ	1.06	0.93-1.21	0.300	0.0000
Random-effects	REML + HKSJ	1.06	0.93-1.21	0.300	0.000005
Fixed-effect	Mantel-Haenszel	1.06	0.90-1.25	0.475	--
Fixed-effect	Inverse-variance	1.06	0.90-1.25	0.475	--

Abbreviations: DL, DerSimonian-Laird; HKSJ, Hartung-Knapp-Sidik-Jonkman; MH, Mantel-Haenszel; OR, odds ratio; REML, restricted maximum likelihood.

eFigure 1. Leave-One-Out Forest Plot for Primary Outcome

[Description: Sequential forest plot showing pooled ORs after excluding each study, demonstrating stability of the primary finding.]

eFigure 2. Forest Plots for Sensitivity Analyses of Secondary Outcomes

[Description: Forest plots for leave-one-out analyses of mortality, sICH, and reperfusion outcomes.]

PRISMA 2020 Checklist

(See accompanying file: prisma-checklist.md)