REVIEW ARTICLE

Direct mechanical thrombectomy with or without thrombolysis for acute ischemic stroke

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[a] Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, No. 45, Changchun Street, Xicheng District, Beijing, 100053, China. China International Neuroscience Institute (China-INI), Beijing, 100053, China.
Contributed equally and co-first author.

[b] Eight-year Program of Clinical Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 1, Shuaifuyuan, Dongcheng District, Beijing, 100730, China.
Contributed equally and co-first author.

[c] Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, No. 45, Changchun Street, Xicheng District, Beijing, 100053, China. China International Neuroscience Institute (China-INI), Beijing, 100053, China.
Contributed equally and co-first author.

[d] Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, No. 45, Changchun Street, Xicheng District, Beijing, 100053, China. China International Neuroscience Institute (China-INI), Beijing, 100053, China.
Corresponding Author.

[e] Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, No. 45, Changchun Street, Xicheng District, Beijing, 100053, China. China International Neuroscience Institute (China-INI), Beijing, 100053, China.
Corresponding Author: xuyueqiao@sina.com

Running title: MT or MT+IVT for acute ischemic stroke

Xuebing Feng[a], Yunying Feng[b], Jie Wang[c], Xin Xu[d], Yueqiao Xu[e]

ABSTRACT

Background: The efficacy of direct mechanical thrombectomy (MT) and thrombectomy combined with intravenous thrombolysis (MT+IVT) in patients with acute ischemic stroke is still unclear. To comprehensively analyze the two strategies, we conducted a meta-analysis of randomized controlled trials (RCTs).

Methods: We retrieved RCTs from Ovid Medline, Embase, and Cochrane Central Register of Controlled Trials to compare favorable functional outcomes (defined as 90-day modified Rankin Scale [mRS] score 0-2), excellent functional outcome (90-day mRS 0-1), 90-day mortality, successful recanalization rate and intracranial hemorrhage rate between MT group and MT+IVT group.

Results: Six RCTs were recruited and published from 2020 to 2023, including 1164 in the MT group and 1170 in the MT+IVT group. There was no significant difference between the MT group and MT + IVT group in 90-day favorable outcome (OR 0.93, 95% CI 0.79-1.09, P=0.37, I^2=0%,) and excellent outcome (OR 0.98, 95% CI 0.82-1.18, P=0.82, I^2=0%). Similarly, there was no significant difference in 90-day mortality (OR 1.08, 95% CI 0.86-1.35, P=0.52, I^2=0%) and symptomatic intracranial hemorrhage (OR 0.82, 95% CI 0.57-1.19, P=0.30, I^2=0%). However, the successful recanalization rate of the MT group was significantly lower than that of the MT+IVT group (OR 0.73, 95% CI 0.57-0.94, P=0.01, I^2=0%).

Conclusions: There was no significant difference in functional outcome and safety endpoints between direct MT and MT+IVT, but the successful recanalization rate of MT+IVT was higher.

Keywords: Mechanical Thrombectomy; Thrombolysis; Ischemic Stroke; Meta-Analysis; RCTs.

INTRODUCTION

Stroke is the second leading cause of death and the third leading cause of disability worldwide. (1) Ischemic stroke accounted for 62•4% of all incident strokes in 2019. (1) Management of acute ischemic stroke mainly focused on intravenous thrombolysis (IVT) and mechanical thrombectomy (MT). IVT was believed to speed up the thrombectomy procedure and improved the chance of successful recanalization. (2) Although IVT has an overall benefit, only 25% of patients with large proximal intracranial vessel occlusion have good outcomes. (3) In addition IVT can lead to intracranial hemorrhage and a potential risk of distal embolism. (4) Evidence shows that beneficial functional outcomes have been observed in MT as an add-on treatment to IVT. (5,

6) Nevertheless, whether the efficacy of direct MT is better or worse than MT with prior IVT remains an issue of contention. (7) Several studies have evaluated the noninferiority of MT alone compared with combined MT+IVT therapy, and previously published meta-analyses conducted on this topic reported contradictory results. (8-11) Four randomized clinical trials (RCTs) (12-15) focusing on MT alone and MT+IVT in acute ischemic stroke were reviewed, including different intervention designs and enrolled populations, yet might be underpowered for addressing the clinical issue. Meanwhile, the recent completion of the DIRECT-SAFE study (16) and the SWIFT-DIRECT trial (17) have added high-quality evidence to this argument. Therefore, it is necessary to update the evidence synthesis and reevaluate the outcomes of MT with or without previous IVT. Here we conduct a systematic review and meta-analysis of the most up-to-date prospective RCT studies evaluating MT with or without IVT for acute ischemic stroke.

METHODS

Our study was conducted and reported based on the updated Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement issued in 2020. (18) The protocol of this systematic review and meta-analysis was registered on PROSPERO (Registration number: CRD42021244541, 22 April 2021). This article is a meta-analysis. The data comes from published articles and does not require ethical approval and written informed consent.

ELIGIBILITY CRITERIA

We included literature on MT and IVT that met the following criteria: 1) the study was designed as a prospective randomized clinical trial; 2) at least ten adult patients with acute large vessel ischemic strokes were assigned in each treatment arm; 3) direct comparison between outcomes of MT without IVT and MT+IVT was reported; and 4) online publication time was later than 1 January 2017.

We excluded non-human studies, case reports, and observational cohort studies to guarantee the high quality of evidence. Editorials, commentaries, or other non-original reports were excluded as well. Studies involving duplicated populations were prudently evaluated, and the one with the full-scale data report was included. Studies were also excluded if other treatments that might affect MT or IVT were applied.

INFORMATION SOURCE AND SEARCH STRATEGY

We developed search strategies for Ovid Medline, Embase, and Cochrane Central Register of Controlled Trials, and conducted comprehensive searches in these three major public electronic databases on clinical medicine and clinical trials (Table S1). Four RCTs on direct MT and MT+IVT was reported in the previously updated meta-analysis, (10) however, no high-quality evidence was found published before 2017. (8) Therefore, the time range limitation of our search was set between 1 January 2017 and 1 January 2023. We further refined our search strategies by performing citation screening through references to previous meta-analyses on this topic, to find more relevant papers. No language restriction was set in our study.

STUDY SELECTION

Article information including titles and abstracts was downloaded from online databases. Before the independent screening by two authors (XF, YF), duplications of the articles had been removed from the retrieved citations. Studies failing to meet the eligibility criteria were eliminated during the initial screening at the title-and-abstract level. Later, all eligible articles were further reviewed by the two authors (XF, YF) at the full-text level separately for final inclusions and exclusions. Disagreements in both initial screening and final screening were resolved by consensus or by consulting a third author (JW).

DATA ITEMS

For each study, we collected the following data: the first author's name, publication year, country, number of participating centers, number of patients, devices used, alteplase dose administrated, demographic information, medical history, occlusion location, and intervention treatment as the baseline data. Baseline features also include the National Institutes of Health Stroke Scale (NIHSS; range, 0 [no symptoms] to 42 [most severe deficits]) and Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range, 0 to 10, with higher scores indicating fewer early ischemic changes) were evaluated. The primary endpoint was functional independence at 90 days evaluated by the modified Rankin Scale (mRS) 0-2. Secondary endpoints were efficacy outcomes including excellent

functional independence with 90-day mRS scores of 0-1 and a successful recanalization rate graded by the expanded Thrombolysis in Cerebral Infarction (eTICI) scale. However, the DIRECT-SAFE trial (16) used a modified Thrombolysis in Cerebral Infarction (mTICI) scale for reperfusion evaluation. Safety endpoints included symptomatic intracranial hemorrhage, 90-day mortality and any intracranial hemorrhage. In the DIRECT-MT trial (14) and MR CLEAN-NO IV trial (12) the symptomatic intracranial hemorrhage was evaluated according to Heidelberg criteria, (19) while the SKIP (13) and the DEVT trials (15) followed the National Institute of Neurological Disorders and Stroke (NINDS) criteria, (20) the remaining two trials (DIRECT-SAFE trial (16) and SWIFT-DIRECT trial (17) were judged according to 4 or more points deterioration of NIHSS.

DATA COLLECTION AND STUDY APPRAISAL

Using a prespecified data collection proforma, two authors (XF, YF) independently extracted data from finally included articles. The research publication information, descriptions of trial design, patient demographic information and medical history, used treatments, and evaluation results of the treatments were collected. Conflicts were resolved by discussion or consulting a third author (JW) of our team.

Two authors (XF, YF) assessed the risk of bias independently with the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. (21) The assessment covered selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. The risk of material bias for each item was assigned as high, low, or unclear according to the reported detail in studies. Disagreements were resolved by a third author (JW).

DATA SYNTHESIS AND ANALYSIS

Statistical analysis was performed based on the included studies using RevMan 5.4 software whose reported outcomes were available for meta-analysis. The combined odds ratios (ORs) with 95% CIs were calculated using individual ORs with 95% CIs from each included study. I^2 was applied to assess potential heterogeneity across studies. A random effect model was used for the result combination. (22) Publication bias was not evaluated due to the limited number of studies included. A two-sided P value less than 0.05 was regarded as statistically significant.

CERTAINTY OF EVIDENCE FOR OUTCOMES

Grading of Recommendations Assessment, Development and Evaluation (GRADE) was assessed for key outcome indicators (clinical outcomes at 90 days, mortality at 90 days, successful recanalization, symptomatic intracranial hemorrhage, and any intracranial hemorrhage) of the included studies. The GRADE system classifies the quality of evidence as high, moderate, low, or very low. The following five factors can reduce the quality of evidence: risk of bias, inconsistency, imprecision, indirectness, and publication bias. We used GradePro (https://gradepro.org) to develop a summary of the findings table.

RESULTS

Study Selection

In total, our search identified 1635 records through electronic search and other sources. After de-duplication, 1284 records were left for the title and abstract assessment, from which 30 full-text articles were obtained for further screening. This review finally included six studies in analyses, which are listed in Table S2 along with the 24 excluded studies. The detailed process of study selection is documented in Fig. 1.

Study Characteristics

All studies included were multicenter, parallel, prospective randomized, open-blinded endpoint clinical trials. We included six RCTs published from 2020 to 2023, including 2334 patients, 1164 in the MT group and 1170 in the MT+IVT group. The experimental centers of the four studies were all in Asia, and three of them included China. Patients were mainly treated with thrombectomy devices approved by the local government, and the treatment alteplase dose was 0.9 mg/kg except in the SKIP trial, where the only approved dosage was 0.6 mg/kg (Table 1). Moreover, this was the only trial that required patients to be 82 years old or younger. The functional independence before stroke was evaluated with the required mRS score of 0-2 in six trials. The initial NIHSS score was equal to 2 or greater in the DIRECT-MT trial (14) and MR CLEAN-NO IV trial, (12) and 5 or greater in the SWIFT-DIRECT trial, (17) and 6 or greater in the

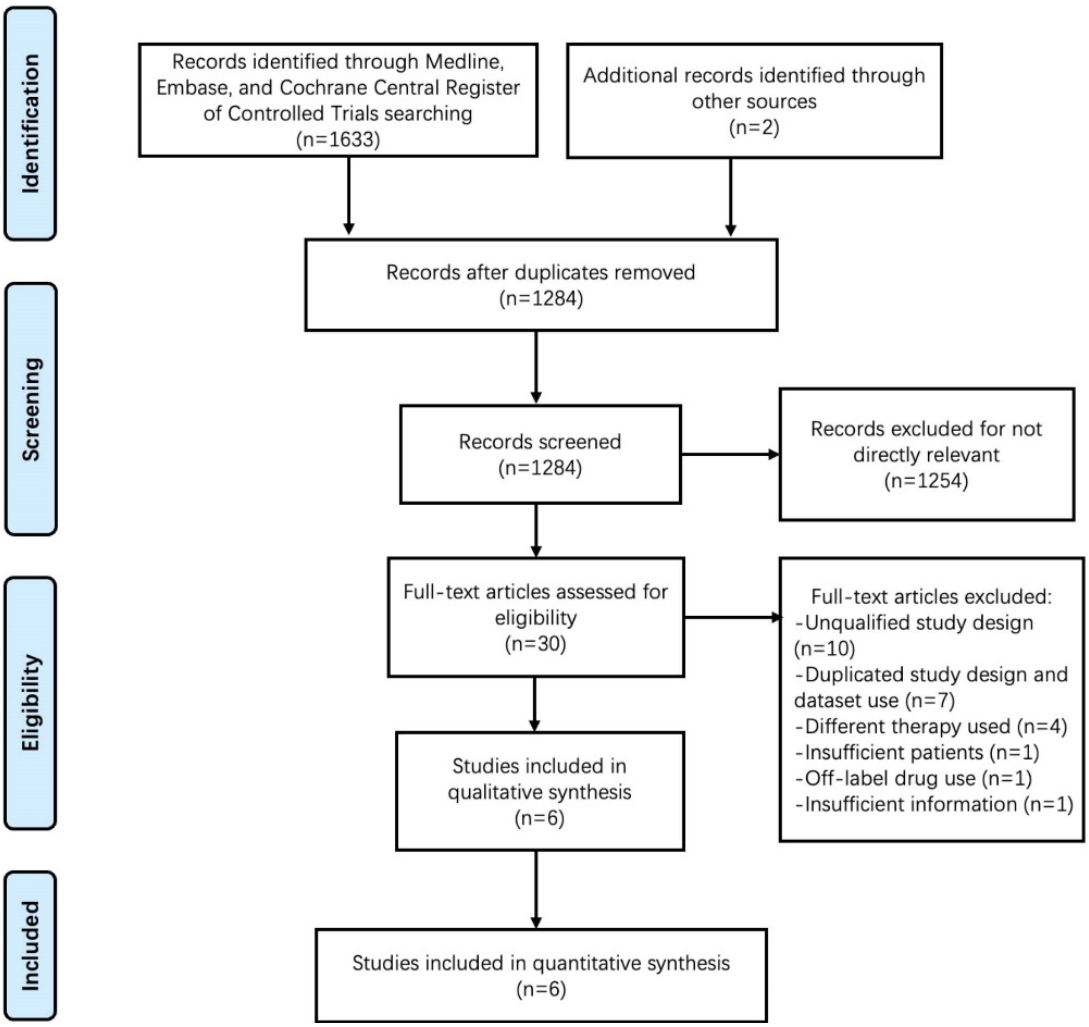

Figure 1. The flowchart of the study selection.

SKIP trial, (13) while this was not required in the DEVT trial (15) and DIRECT-SAFE trial. (16) The ASPECTS was an enrolment criterion for the SKIP (13) and SWIFT-DIRECT (17) study, which were 4 points and 6 points higher, respectively.

Characteristics of Included Patients

The baseline characteristics of included patients were similar between arms across studies (Table 1). The median age of patients with MT in all experiments ranged from 69 to 74 years old, of which men accounted for 48% to 59%. The sex distribution was approximately 1:1 in all studies. However, in the MT+IVT arm of the SKIP trial, (13) the percentage of males was 70%. In the SWIFT-DIRECT experiment, (17) the proportion of the enrolled patients undergoing atrial fibrillation was relatively less than others (8% vs 11% in the MT group vs MT+IVT group). Patients with a history of hyperlipidemia accounted for less percentage in the DIRECT-MT trail (14) than in other trials (4% vs 4% in the MT group vs MT+IVT group). The percentage of patients smoking in the SKIP trial (13) was higher than that in other trials. The severity of stroke ranged from 15-19, which indicated severe stroke in the NIHSS. In the six trials, 50% to 84% of the occlusions were located in the M1 segment of the middle cerebral artery (MCA), which was higher than the incidence of internal carotid artery (ICA) occlusion. In the DEVT trial, (15) the time from stroke onset to randomization, from onset to groin puncture, or from onset to recanalization was longer than in the other five trials, while the time from stroke onset to groin puncture was the shortest in the MR CLEAN-NO IV trial. (12)

Trial *	SKIP (13)	MR CLEAN-NO IV (12)	DIRECT-MT (14)	DIRECT-SAFE (16)	DEVT (15)	SWIFT-DIRECT (17)
Author	Kentaro Suzuki	Natalie E. LeCouffe	P. Yang	Peter J. Mitchell	Wenjie Zi	Urs Fischer
Publication time	2021	2021	2020	2022	2021	2022
Country	Japan	Europe	China	Australia, New Zealand, China and Vietnam	China	Europe and Canada
Center, n	23	20	41	25	33	48
Device	CTA/MRA	CTA	CTA	CT/CTA/MRI/MRA	CTA/MRA	CTA/MRA
alteplase dose	0.6mg/kg	0.9mg/kg	0.9mg/kg	0.9mg/kg	0.9mg/kg	0.9mg/kg
Number of included patients	101/103	273/266	327/329	146/147	116/118	201/207
Age (years), Median (range)	74(67-80)/76(67-80)	72(62-80)/69(61-77)	69(61-76)/69(61-76)	70(61-78)/69(60-79)	70(60-77)/70(60-78)	73(64-81)/72(65-81)
Gender, male, n (%)	56(55%)/72(70%)	161(59%)/144(54%)	189(58%)/181(55%)	78(53%)/88(60%)	66(57%)/66(56%)	96(48%)/103(50%)
Atrial fibrillation, n (%)	57(56%)/64(62%)	86(32%)/63(24%)	152(47%)/149(45%)	46(32%)/34(23%)	62(54%)/62(53%)	17(8%)/22(11%)
Previous ischemic stroke, n(%)	12(12%)/14(14%)	47(17%)/44(17%)	43(13%)/47(14%)	26(18%)/18(12%)	14(12%)/19(16%)	21(10%)/20(10%)
Hypertension, n (%)	61(60%)/61(59%)	121(44%)/139(53%)	193(59%)/201(61%)	86(59%)/89(61%)	69(60%)/74(63%)	121(60%)/118(57%)
Diabetes mellitus, n (%)	16(16%)/17(17%)	540(15%)/50(19%)	59(18%)/65(20%)	NA/NA	25(22%)/20(17%)	NA/NA
Smoking, n (%)	42(42%)/54(52%)	73(28%)/66(25%)	73(22%)/68(20%)	NA/NA	28(24%)/29(25%)	NA/NA
Hyperlipidemia, n (%)	30(30%)/37(36%)	79(29%)/73(27%)	13(4%)/14(4%)	NA/NA	18(16%)/22(19%)	60(30%)/71(34%)
Admission NIHSS, Median (range) †	19(13-23)/17(12-22)	16(10-20)/16(10-20)	17(12-21)/17(14-22)	15(11-20)/15(10-20)	16(12-20)/16(13-20)	17(13-20)/17(12-20)
Admission ASPECTS score, Median (range) ‡	7 (6-9)/8 (6-9)	NA/NA	9 (7-10)/9(7-10)	NA/NA	8 (7-9)/8 (7-9)	NA/NA
ICA, n (%)	41 (41%)/36 (35%)	68(25%)/50(19%)	112(35%)/114(35%)	33(23%)/31(21%)	18(16%)/17 (14%)	57(28%)/60 (29%)
M1, n (%)	60 (59%)/67 (65%)	156(57%)/174(65%)	161(50%)/178(55%)	80(55%)/83(57%)	95(82%)/99 (84%)	133(66%)/136 (66%)
Onset to puncture, Median (range)	NA/NA	130(103-180)/ 135(106-185)	NA/NA	NA/NA	200(155-247)/ 210(179-255)	NA/NA
Onset to randomization, Mean ± SD, Median (range)	129±80/136±83	94(69-137)/ 93(71-152)	167(125-206)/ 177(126-215)	136(110-186)/ 151(108-204)	170(129-204)/ 168(144-216)	123(99-163)/ 135(106-171)
From randomization to revascularization, Median (range)	NA/NA	NA/NA	102(74-141)/ 59(72-131)	87(59-129)/90(64-121)	111(84-150)/ 106(75-154)	NA/NA
From hospital admission to start of alteplase, Median (range)	NA/NA	NA/31(24-44)	NA/59(45-78)	NA/64 (47-87)	NA/61(49-81)	NA/55 (38-71)

Table 1. Characteristics of included studies and patients.

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*Trial name: DIRECT-MT: Direct Intraarterial Thrombectomy to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: a Multicenter Randomized Clinical Trial; DEVT: Direct Endovascular Thrombectomy vs Combined IVT and Endovascular Thrombectomy for Patients with Acute Large Vessel Occlusion in the Anterior Circulation; SKIP: Direct Mechanical Thrombectomy in Acute LVO Stroke; MR CLEAN-NO IV: Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands)-NO IV; DIRECT-SAFE: A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval versus Standard Bridging Therapy; SWIFT-DIRECT: Thrombectomy alone would be non-inferior to intravenous alteplase plus thrombectomy in directly admitted patients presenting with an acute ischaemic stroke.

Abbreviation Description: CT: Computed tomography; CTA: Computed tomography angiography; MRI: Magnetic Resonance Imagin; MRA: magnetic resonance angiography;† NIHSS: National Institutes of Health Stroke Scale (range, 0 [no symptoms] to 42 [most severe deficits]); ‡ ASPECT: Alberta Stroke Program Early Computed Tomography Score (range, 0 to 10, with higher scores indicating fewer early ischemic changes); ICA: internal carotid artery; M1: the first segments of the middle cerebral artery; NA: not applicable.

Risk of Bias Within Studies

The overall risk of bias was moderate among different trials (Figure S1). Random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting could be considered low risk among all the six trials. Considering the study design of open-blind endpoint design, blinding of participants and personnel were all categorized as high risk in these six trials. The DEVT trial (15) stopped early as the first interim analysis after 20% of participants of the maximum sample size recruited confirmed that the noninferiority test had reached the prespecified early termination boundary. All the studies were prospectively registered, while the primary outcome of the SKIP trial (13) was changed from superiority for poor mRS outcome to noninferiority for favorable outcomes before any patient's data was reviewed. All the studies were funded by public funds that played no role in the whole process of study.

Clinical outcomes at 90 days

Rates of functional independence were evaluated in all six trials, defined as mRS scores 0-2. Overall, 1165 out of 2332 patients (50.0%) reached functional independence at 90 days. There was no significant difference in the functional independence rates between patients randomly divided into MT group and MT+IVT group (OR 0.93, 95% CI 0.79-1.09, P=0.37, I^2=0%, Fig. 2). Excellent functional outcomes defined as mRS score 0-1 also showed no statistical difference in the two groups (OR 0.98, 95% CI 0.82-1.18, P=0.82, I^2=0%, Fig. 3).

Mortality at 90 days

The Overall mortality rate at 90 days as a secondary clinical outcome was 15.5%, of which the mortality rate of the MT group was 16.0%, and the ratio of MT+IVT group was 15.0%, without significant differences between the MT arm and the MT+IVT arm (OR 1.08, 95% CI, 0.86-1.35, P=0.52, I^2=0%, Fig. 4).

Successful Recanalization

Successful recanalization was defined as modified thrombolysis in Cerebral Ischemia score 2b-3, evaluated in all six trials. The successful recanalization rate was 84.2% in the MT group and 88.0% in the MT + IVT group. The successful recanalization rate of the MT group was significantly lower than that of the MT+IVT group (OR 0.73, 95% CI 0.57-0.94, P=0.01, I^2=0%, Fig. 5).

Symptomatic Intracranial Hemorrhage

Rates of symptomatic intracranial hemorrhage were reported in all six studies, with an overall incidence rate of 5.2%. Symptomatic intracranial hemorrhage was nominally more prevalent in MT+IVT patients and the bleeding risk was higher than that in the MT group (5.7% vs 4.7%). However, it does not reach statistical significance between the two groups (OR 0.82, 95% CI 0.57-1.19, P=0.30, I^2=0%, Fig. 6).

Any intracranial hemorrhage

In addition, the incidence of intracranial hemorrhage in MT group was significantly lower than that in MT group, with statistical significance (31.7% vs. 36.4%, OR 0.80, 95% CI 0.66-0.97, P=0.03, I^2=16%, Fig.7).

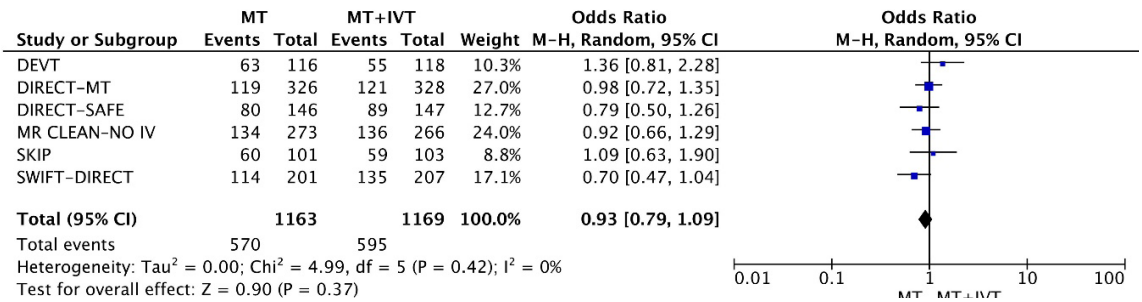

Figure 2. mRS 0-2 at 90 days.

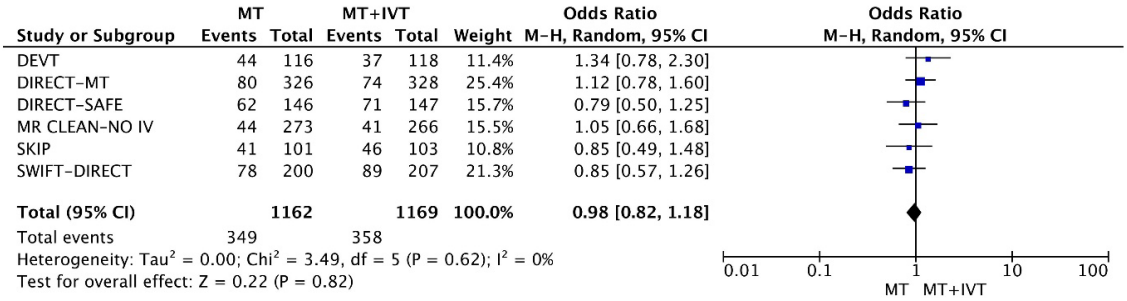

Figure 3. mRS 0-1 at 90 days.

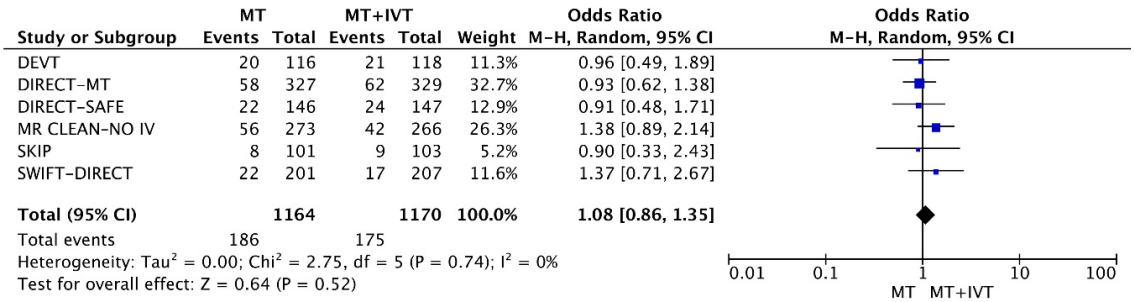

Figure 4. Mortality at 90 days.

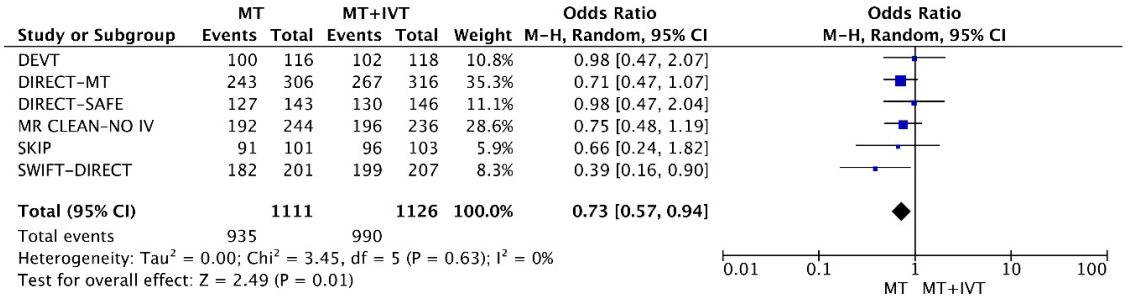

Figure 5. Successful recanalization defined as mTICI 2b-3.

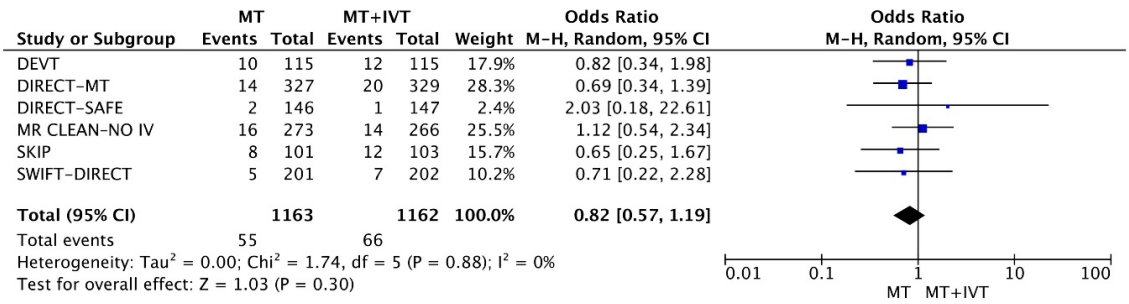

Figure 6. Symptomatic intracranial hemorrhage.

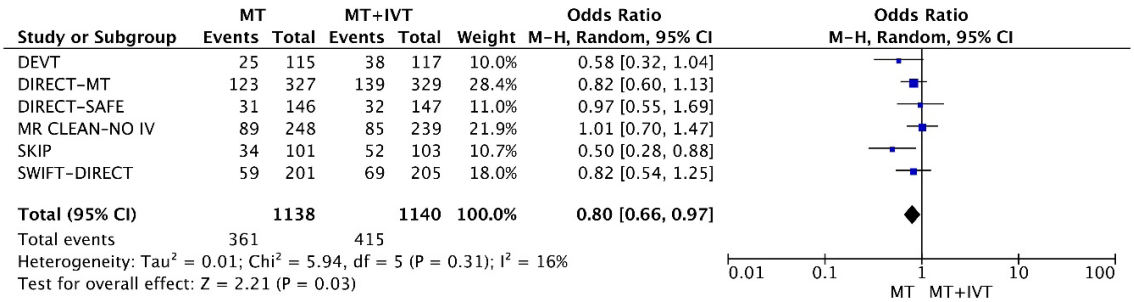

Figure 7. Any intracranial hemorrhage

Additional analysis

We conducted an extensive subgroup analysis of patients with 90-day mRS Scores of 0 to 2. Subgroup analysis was based on geographic region, there were similarities between the non-Asian subgroup (55.2% in MT group versus 58.3% in MT+IVT group) and the Asians subgroup (43.4% in MT group versus 44.3% in MT+IVT group), without showing a statistically significant heterogeneity between the subgroups (Chi^2=0.01, P=0.94, I^2=0%, Figure S2).

GRADE evaluation

Clinical outcomes at 90 days defined as mRS scores 0-2 and 0-1, mortality at 90 days, successful recanalization, symptomatic intracranial hemorrhage and any intracranial hemorrhage were all rated as moderate certainty of evidence (Table 2).

DISCUSSION

This meta-analysis, based on six published multicenter and prospective RCTs, demonstrated no significant differences in 90-day functional outcomes between the MT group and the MT+IVT group. A higher rate of successful recanalization rate was found in the MT+IVT group than MT group. Although IVT before MT did not statistically increase the risk of 90-day mortality or symptomatic intracranial hemorrhage, there was a greater risk of any bleeding occurring. Safety indicators were similar to clinical outcomes in all eligible patients with acute ischemic stroke due to large vessel occlusion and receiving different treatments.

Controversy still exists in previous meta-analyses on the application of IVT before MT. The analysis of 12 studies (including 5 RCTs and 7 prospective cohort studies) published by Phan et al (23) showed that the MT+IVT group unexpectedly has a lower reperfusion chance than the MT group and increases the risk of bleeding. Yarbrough et al (24) reported MT improves good outcomes in anterior circulation stroke patients. While, the research published by Mistry et al (8) showed that the MT + IVT group was associated with better functional outcomes, lower mortality, a higher rate of successful recanalization, and required lower number of device passes than the direct MT group. Other research, such as Katsanos et al (4), demonstrated comparable functional outcomes between the two modalities. But a major concern for these meta-analyses was the inclusion of observational

Outcome Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		MT+IVT	MT	Difference	
mRS score 0-2 at 90 days 2332 (6)	OR 0.93 (0.79 - 1.09)	50.9%	49.1% (45 - 53)	1.8% (5.9 to-2.2)	⊕⊕⊕◯ Moderate[a]
mRS score 0-1 at 90 days 2331 (6)	OR 0.98 (0.82 - 1.18)	30.6%	30.2% (26.6 - 34.2)	0.4% (4 to-3.6)	⊕⊕⊕◯ Moderate[a]
mortality at 90 days 2334 (6)	OR 1.08 (0.86 - 1.35)	15.0%	16.0% (13.1 - 19.2)	-1.0% (1.8 to-4.2)	⊕⊕⊕◯ Moderate[a]
successful recanalization 2b-3 2237 (6)	OR 0.73 (0.57 - 0.94)	87.9%	84.2% (80.6 - 87.2)	3.8% (7.3 to 0.7	⊕⊕⊕◯ Moderate[a]
symptomatic intracranial hemorrhage 2325 (6)	OR 0.82 (0.57 - 1.19)	5.7%	4.7% (3.3 - 6.7)	1.0% (2.4 to-1)	⊕⊕⊕◯ Moderate[a]
any intracranial hemorrhage 2278 (6)	OR 0.80 (0.66 - 0.97)	36.4%	31.4% (27.4 - 35.7)	5.0% (9 to 0.7)	⊕⊕⊕◯ Moderate[a]

Table 2. GRADE evaluation.

https://doi.org/10.37819/hb.1.1811

studies, which were vulnerable to selection bias. Thus, an updated meta-analysis based on high-quality studies, especially RCTs, was necessary. This meta-analysis showed that the rate of successful recanalization in 6 RCTs reported numerical differences in the same direction, which was beneficial for intravenous alteplase plus thrombectomy, especially in the SWIFT-DIRECT trial. The inclusion criteria of the SWIFT-DIRECT trial specifically excluded patients with M2 segment occlusion of the middle cerebral artery, cervical vessel tortuosity, and multiple vessel occlusions compared to other trials. Moreover, another potential reason for the high reperfusion rate of MT+IVT was that the current study included only a minority of patients treated with aspiration, avoiding the potential negative effects of aspiration plus intravenous alteplase. The use of stent retrievers with concomitant proximal flow-arrest or distal aspiration seemed to translate into an overall favorable reperfusion rate. Excellent reperfusion, defined as eTICI 2c-3, may be better associated with improved neurological outcomes than successful reperfusion, but there was insufficient data for pooled analysis.

Several previous studies have reported on the meta-analysis of RCTs. Our results are consistent with recent studies involving only RCT, which have expressed a neutral attitude towards functional outcomes and safety concerning patients with acute large vessel occlusion stroke who receive systemic thrombolysis or not. (10, 25)Without affecting the prognosis, bridging therapy has a higher successful recanalization rate than direct thrombectomy. Increasing systemic thrombolysis may also be beneficial to multifocal ischemia or difficult-to-reach thrombi, such as in distal occlusion, vascular tortuosity, high tandem stenosis, and arterial access difficulties, to improve the recanalization rate. Thus, the current guidelines still recommend the use of bridging thrombolysis before MT when suitable. (26)

Determining how to choose a more suitable treatment modality for stroke patients is crucial. Many factors need to be considered before deciding whether patients should receive IVT in the nearest center rather than being immediately transferred to an MT-capable center. MT+IVT is recommended for use in the nearest centers that need a further transfer of patients, and as a first-line treatment, IVT can promote MT and recanalize distal thrombi that are accessible to intravascular devices. (2, 11) However, the reason why MT research abandons IVT is that thrombolysis prolongs the treatment time and increases the risk of complications. (27) On this issue, the RACECAT trial (28) has shown that there was no difference between the two treatments in clinical outcomes. Meanwhile, some researchers argued that thrombolysis was suitable for centers that were unable to perform MT or nearest, and it was reasonable to choose bridging thrombolysis for patients who were unlikely to suffer from intracranial hemorrhage. Whereas for patients with acute large-vessel occlusion arriving at a primary stroke center, the chance of successful recanalization may be increased if the centers choose to use IVT, and previous studies have suggested that stroke centers are more likely to choose direct embolectomy.

This meta-analysis still had several limitations. Firstly, selecting patients and medical centers was an intention to treat, which might exaggerate the magnitude of effects in the real world. Secondly, longer follow-ups were required for spontaneous neurological recovery to attain maximal recovery potential and to better understand the long-term functional outcomes in both arms. (29) Thirdly, another limitation was the overall risk of bias that originated either by study design, such as failure of allocation concealment or by early termination. Fourthly, due to the lack of unified records of the onset time period, we did not conduct further subgroup analysis on the reasons for the successful recanalization rate. Therefore, there remains a possibility that the available information is not definitive enough.

CONCLUSION

The meta-analysis of six published RCTs shows that compared with MT+IVT, direct MT has no significant difference in functional independence, mortality rates, and symptomatic intracranial hemorrhage. However, the above results contrast with some previous research and even results in initial trials are shown that the MT group is inferior to the MT+IVT group in terms of successful recanalization rate, so further RCTs are required to draw more powerful conclusions.

DECLARATIONS

Ethics approval and consent to participate

This article is a meta-analysis. The data comes from published articles and does not require ethical approval and written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article and supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors participated in the manuscript's concept, design, analysis, writing, or revision. All authors participated in the reported analyses and the interpretation of results relevant to their domain of interest. Xuebing Feng and Yunying Feng prepared the draft manuscript and coordinated its finalization. Xuebing Feng and Jie Wang performed the statistical analyses and drafting of tables and figures. Yueqiao Xu and Xin Xu revised the manuscript and gave support in statistical analyses, drafting of figures and review. All authors were responsible for the acquisition of data and revision of the manuscript.

Acknowledgments

None. ♦

LIST OF ABBREVIATIONS

Trial name

DIRECT-MT: Direct Intraarterial Thrombectomy to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: a Multicenter Randomized Clinical Trial;

DEVT: Direct Endovascular Thrombectomy vs Combined IVT and Endovascular Thrombectomy for Patients with Acute Large Vessel Occlusion in the Anterior Circulation;

SKIP: Direct Mechanical Thrombectomy in Acute LVO Stroke;

MR CLEAN-NO IV: Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands)–NO IV;

DIRECT-SAFE: A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval versus Standard Bridging Therapy;

SWIFT-DIRECT: Thrombectomy alone would be non-inferior to intravenous alteplase plus thrombectomy in directly admitted patients presenting with an acute ischemic stroke.

Abbreviation description

MT: direct mechanical thrombectomy;

MT+IVT: mechanical thrombectomy following intravenous thrombolysis;

CT: Computed tomography;

CTA: Computed tomography angiography;

MRI: Magnetic Resonance imaging;

MRA: magnetic resonance angiography;

NIHSS: National Institutes of Health Stroke Scale;

ASPECT: Alberta Stroke Program Early Computed Tomography Score;

ICA: internal carotid artery;

MCA: middle cerebral artery;

M1: the first segments of the middle cerebral artery;

NA: not applicable;

mRS: modified Ranking Scale;

eTICI: extended/expanded thrombolysis in Cerebral Ischemia;

mTICI: means modified thrombolysis in Cerebral Ischemia.

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SUPPLEMENTARY MATERIALS

Table S1. Sources searched and search strategies

Databases	Search terms	Amount
Medline. Date of search 15 July 2022	1. exp Stroke/ 2. exp cerebrovascular accident/ 3. (stroke or strokes or apoplexy or "cerebrovascular accident*" or ((cerebrovascular or cerebral or brain) adj3 (infarct or insult or insultus or accident* or "blood flow disturbance*")) or apoplexia or "brain ischemic attack*" or "brain ischaemic attack*" or "brain attack*" or "cerebral vascular insufficiency" or (cerebrovascular adj3 (insufficiency or arrest or failure or injur* or trauma)) or "cerebrum vascular accident*" or "ischemic cerebral attack*").mp. 4. or/1-3 5. exp Brain Ischemia/ 6. ischemia/ 7. (ischem* or ischaem* or "circulation disorder*").mp. 8. (brain or cerebral* or cerebrovascular*).ti,ab,sh,hw,kw. 9. (6 or 7) and 8 10. 5 or 9 11. exp acute disease/ 12. acute.mp. 13. 11 or 12 14. 4 and 10 and 13 15. exp mechanical thrombolysis/ 16. exp embolectomy/ 17. exp thrombectomy/ 18. (mechanical adj3 (thrombectom* or thromboembolectom* or thrombo- embolectom* or thrombolys* or remov* or disrupt* or clot* or embolectom* or recanalis* or recanaliz* or retriev*)).tw. 19. neurothrombectom*.tw. 20. merci.tw. 21. penumbra system.tw. 22. solitaire.tw. 23. trevo.tw. 24. or/15-23 25. exp Thrombolytic Therapy/ 26. exp Fibrinolytic Agents/ 27. exp Urokinase-Type Plasminogen Activator/ 28. exp urokinase/ 29. exp streptokinase/ 30. exp Tissue Plasminogen Activator/ 31. exp alteplase/ 32. exp tenecteplase/ 33. (thrombolytic or thrombolysis or thrombolyses or fibrinoly* or local or "intra-arterial*" or urokinase or prourokinase or "plasminogen activat*" or streptokinase* or antithrombotic or "anti-thrombotic" or antithrombic or "anti-thrombic" or fibrinolyser or fibrolytic or antithrombogenic or "anti-thrombogenic" or "u-pa" or abbokinase or renokinase or actosolv or alphakinase or corase or kinlytic or medacinase or "prourokinase" or rheotromb or ukidan or urokine or avelizin or awelysin or celiase or "k-nase" or kabikinase or kinaysin or plasminokinase or plasmokinase or streptase or streptodecase or streptodekaza or zykinase or kabivitrum or distreptase or tPA or "tissue plasminogen activator"	460

Databases	Search terms	Amount
	or alteplase or reteplase or tenecteplase or "lysatec rt-pa" or activase or "tissue activator d-44" or tisokinase or ttpa or "lysatec rtpa" or actilyse or ak124 or "ak 124" or angiochinase or angiokinase or hapase or actilyse or activacin or atlepase or ecokinase or rapilysin or retavase or metalyse or TNKase).mp. 34. or/25-33 35. 24 and 34 36. randomized controlled trial.pt. 37. controlled clinical trial.pt. 38. randomized.ab. 39. placebo.ab. 40. clinical trials as topic.sh. 41. randomly.ab. 42. trial.ti. 43. or/36-42 44. and/14,35,43 45. exp animals/ not humans.sh. 46. 44 not 45 47. limit 46 to yr="2017 -Current"	
Embase. Date of search 15 July 2022	1. 'cerebrovascular accident'/exp 2. stroke OR strokes OR apoplexy OR 'cerebrovascular accident*' OR ((cerebrovascular OR cerebral OR brain) NEAR/3 (infarct OR insult OR insultus OR accident* OR 'blood flow disturbance*')) OR apoplexia OR 'brain ischemic attack*' OR 'brain ischaemic attack*' OR 'brain attack*' OR 'cerebral vascular insufficiency' OR (cerebrovascular NEAR/3 (insufficiency OR arrest OR failure OR injur* OR trauma)) OR 'cerebrum vascular accident*' OR 'ischemic cerebral attack*' 3. #1 OR #2 4. 'brain ischemia'/exp 5. 'ischemia'/de 6. ischem* OR ischaem* OR 'circulation disorder*' 7. brain:ti,ab,kw,de OR cerebral*:ti,ab,kw,de OR cerebrovascular*:ti,ab,kw,de 8. (#5 OR #6) AND #7 9. #4 OR #8 10. 'acute disease'/exp 11. acute 12. #10 OR #11 13. #3 AND #9 AND #12 14. 'mechanical thrombectomy'/exp 15. 'embolectomy'/exp 16. 'thrombectomy'/exp 17. (mechanical NEAR/3 (thrombectom* OR thromboembolectom* OR 'thrombo embolectom*' OR thrombolys* OR remov* OR disrupt* OR clot* OR embolectom* OR recanalis* OR recanaliz* OR retriev*)):ab,ti,tn 18. neurothrombectom*:ab,ti,tn 19. merci:ab,ti,tn 20. 'penumbra system':ab,ti,tn 21. solitaire:ab,ti,tn 22. trevo:ab,ti,tn 23. #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 24. 'fibrinolytic therapy'/exp	951

Databases	Search terms	Amount
	25. 'fibrinolytic agent'/exp 26. 'urokinase'/exp 27. 'streptokinase'/exp 28. 'tissue plasminogen activator'/exp 29. 'alteplase'/exp 30. 'reteplase'/exp 31. 'tenecteplase'/exp 32. thrombolytic OR thrombolysis OR thrombolyses OR fibrinoly* OR local OR 'intra-arterial*' OR urokinase OR prourokinase OR 'plasminogen activat*' OR streptokinase* OR antithrombotic OR 'anti-thrombotic' OR antithrombic OR 'anti-thrombic' OR fibrinolyser OR fibrolytic OR antithrombogenic OR 'anti-thrombogenic' OR 'u-pa' OR abbokinase OR renokinase OR actosolv OR alphakinase OR corase OR kinlytic OR medacinase OR 'pro urokinase' OR rheotromb OR ukidan OR urokine OR avelizin OR awelysin OR celiase OR 'knase' OR kabikinase OR kinaysin OR plasminokinase OR plasmokinase OR streptase OR streptodecase OR streptodekaza OR zykinase OR kabivitrum OR distreptase OR tpa OR 'tissue plasminogen activator' OR alteplase OR reteplase OR tenecteplase OR 'lysatec rtpa' OR activase OR 'tissue activator d-44' OR tisokinase OR ttpa OR 'lysatec rtpa' OR ak124 OR 'ak 124' OR angiochinase OR angiokinase OR hapase OR actilyse OR activacin OR atlepase OR ecokinase OR rapilysin OR retavase OR metalyse OR tnkase 33. #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 34. #23 AND #33 35. [randomized controlled trial]/lim 36. [controlled clinical trial]/lim 37. randomized:ab 38. placebo:ab 39. 'clinical trial (topic)'/exp 40. randomly:ab 41. trial:ti 42. #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 43. #13 AND #34 AND #42 44. 'animal'/exp NOT 'human'/exp 45. #43 NOT #44 46. #45 AND [2017-2021]/py	
Cochrane Central Register of Controlled Trials. Date of search 15 July 2022	1. MESH DESCRIPTOR stroke EXPLODE ALL TREES 2. MESH DESCRIPTOR cerebrovascular accident EXPLODE ALL TREES 3. stroke or strokes or apoplexy or cerebrovascular accident* or ((cerebrovascular or cerebral or brain) ADJ3 (infarct or insult or insultus or accident* or blood flow disturbance*)) or apoplexia or brain ischemic attack* or brain ischaemic attack* or brain attack* or cerebral vascular insufficiency or (cerebrovascular ADJ3 (insufficiency or arrest or failure or injur* or trauma)) or cerebrum vascular accident* or ischemic cerebral attack* 4. #1 OR #2 OR #3 5. MESH DESCRIPTOR Brain Ischemia EXPLODE ALL TREES 6. MESH DESCRIPTOR ischemia 7. ischem* or ischaem* or circulation disorder* 8. (brain or cerebral* or cerebrovascular*):MH,TI,AB,KY	222

Databases	Search terms	Amount
	9. (#6 OR #7) AND #8 10. #5 OR #9 11. MESH DESCRIPTOR acute disease EXPLODE ALL TREES 12. acute 13. #11 OR #12 14. #4 AND #10 AND #13 15. MESH DESCRIPTOR mechanical thrombolysis EXPLODE ALL TREES 16. MESH DESCRIPTOR embolectomy EXPLODE ALL TREES 17. MESH DESCRIPTOR thrombectomy EXPLODE ALL TREES 18. (mechanical ADJ3 (thrombectom* or thromboembolectom* or thrombo-embolectom* or thrombolys* or remov* or disrupt* or clot* or embolectom* or recanalis* or recanaliz* or retriev*)):TI,AB,KY 19. neurothrombectom*:TI,AB,KY 20. merci:TI,AB,KY 21. (penumbra system):TI,AB,KY 22. solitaire:TI,AB,KY 23. trevo:TI,AB,KY 24. #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 25. MESH DESCRIPTOR Thrombolytic Therapy EXPLODE ALL TREES 26. MESH DESCRIPTOR Fibrinolytic Agents EXPLODE ALL TREES 27. MESH DESCRIPTOR Urokinase-Type Plasminogen Activator EXPLODE ALL TREES 28. MESH DESCRIPTOR urokinase EXPLODE ALL TREES 29. MESH DESCRIPTOR streptokinase EXPLODE ALL TREES 30. MESH DESCRIPTOR Tissue Plasminogen Activator EXPLODE ALL TREES 31. MESH DESCRIPTOR alteplase EXPLODE ALL TREES 32. MESH DESCRIPTOR reteplase EXPLODE ALL TREES 33. MESH DESCRIPTOR tenecteplase EXPLODE ALL TREES 34. thrombolytic or thrombolysis or thrombolyses or fibrinoly* or local or intra-arterial* or urokinase or prourokinase or plasminogen activat* or streptokinase* or antithrombotic or anti-thrombotic or antithrombic or anti-thrombic or fibrinolyser or fibrolytic or antithrombogenic or anti-thrombogenic or u-pa or abbokinase or renokinase or actosolv or alphakinase or corase or kinlytic or medacinase or pro urokinase or rheotromb or ukidan or urokine or avelizin or awelysin or celiase or k-nase or kabikinase or kinaysin or plasminokinase or plasmokinase or streptase or streptodecase or streptodekaza or zykinase or kabivitrum or distreptase or tPA or tissue plasminogen activator or alteplase or reteplase or tenecteplase or lysatec rt-pa or activase or tissue activator d-44 or tisokinase or ttpa or lysatec rtpa or actilyse or ak124 or ak 124 or angiochinase or angiokinase or hapase or actilyse or activacin or atlepase or cokinase or rapilysin or retavase or metalyse or TNKase 35. #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 36. #24 AND #35 37. 2017 TO 2022:YR 38. 38 #36 AND #37	
Total		**1.633**
Total after duplication		**1.284**

Table S2. Study selection.

References to studies included in this review

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(10346):104-1.

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Figure S1. Risk of bias summary.

Figure S2. Subgroup analysis of patients with mRS of 0 to 2 by geographic region

Study or Subgroup	MT Events	MT Total	MT+IVT Events	MT+IVT Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Non-Asians						
DIRECT-SAFE	57	79	50	78	9.3%	1.45 [0.74, 2.85]
MR CLEAN-NO IV	134	273	136	266	19.5%	0.92 [0.66, 1.29]
SWIFT-DIRECT	114	201	135	207	17.0%	0.70 [0.47, 1.04]
Subtotal (95% CI)		**553**		**551**	**45.7%**	**0.91 [0.65, 1.27]**
Total events	305		321			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 3.46$, df = 2 (P = 0.18); $I^2 = 42\%$						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.1.2 Asians						
DEVT	63	116	55	118	13.1%	1.36 [0.81, 2.28]
DIRECT-MT	119	326	121	328	20.3%	0.98 [0.72, 1.35]
DIRECT-SAFE	23	67	39	69	8.9%	0.40 [0.20, 0.80]
SKIP	60	101	59	103	11.9%	1.09 [0.63, 1.90]
Subtotal (95% CI)		**610**		**618**	**54.3%**	**0.92 [0.61, 1.39]**
Total events	265		274			
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 8.05$, df = 3 (P = 0.05); $I^2 = 63\%$						
Test for overall effect: Z = 0.38 (P = 0.70)						
Total (95% CI)		**1163**		**1169**	**100.0%**	**0.93 [0.72, 1.19]**
Total events	570		595			
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 11.80$, df = 6 (P = 0.07); $I^2 = 49\%$						
Test for overall effect: Z = 0.61 (P = 0.54)						
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.94), $I^2 = 0\%$