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Endovascular thrombectomy with versus without intravenous thrombolysis for acute ischaemic stroke (Review)

Gottlieb M, Carlson JN, Westrick J, Peksa GD

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[Intervention Review]

Endovascular thrombectomy with versus without intravenous thrombolysis for acute ischaemic stroke

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ABSTRACT

Rationale

Acute ischaemic stroke is a major cause of death and disability worldwide. Once diagnosed, treatment is generally limited to intravenous thrombolysis (IVT), endovascular thrombectomy, or both. Intravenous thrombolysis has theoretical benefits (enhancing reperfusion, dissolving smaller thrombi) and harms (delaying time to endovascular intervention, allergic reaction, increased bleeding risk).

Objectives

To assess the effects of endovascular thrombectomy with IVT versus without IVT on functional independence (defined as a modified Rankin Scale score (mRS) < 3) within 90 days in people with acute ischaemic stroke.

Search methods

We searched CENTRAL, MEDLINE, Embase, Scopus, LILACS, Google Scholar, the International HTA database, and two trial registries to November 2023.

Eligibility criteria

We included randomised controlled trials of adults with acute ischaemic stroke who received endovascular therapy and were randomised to either intravenous thrombolysis within 4.5 hours or a control.

Outcomes

Outcomes were: functional independence (mRS score < 3), excellent functional outcome (mRS score < 2), mortality, asymptomatic intracranial haemorrhage, symptomatic intracranial haemorrhage, successful revascularisation (thrombolysis in cerebral infarction (TICI) grades 2b to 3), and complete revascularisation (TICI grade 3 only), within 90 days.

Risk of bias

We used the Cochrane RoB 2 tool to assess the following potential sources of bias for each outcome: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result.

Synthesis methods

We pooled outcome data using the random-effects model and performed meta-analyses using the Mantel-Haenszel method. We assessed the statistical heterogeneity of pooled data by visually inspecting forest plots to consider the direction and magnitude of effects, and used the Chi^2 test and I^2 statistic to quantify the heterogeneity. We used GRADE to assess the certainty of evidence.

Included studies

We included six studies, with a total of 2336 participants (1166 control and 1170 intervention). The mean age was 71 years. There were 1034 women and 1302 men. Four studies used alteplase 0.9 mg/kg, one study used alteplase 0.6 mg/kg, and one study used either alteplase 0.9 mg/kg or tenecteplase 0.25 mg/kg. There were no important variations in the outcomes reported across studies.

Synthesis of results

All six studies were at overall low risk of bias for each outcome.

There was probably little to no difference in functional independence between the IVT and control groups (risk ratio (RR) 1.03, 95% confidence interval (CI) 0.92 to 1.14; P = 0.62; 6 studies, 2336 participants; moderate-certainty evidence).

There was no evidence of a difference in excellent functional outcome between the IVT and control groups (RR 0.99, 95% CI 0.92 to 1.05; P = 0.67; 6 studies, 2336 participants; high-certainty evidence).

There was no evidence of a difference in mortality between the IVT and control groups (RR 0.94, 95% CI 0.78 to 1.14; P = 0.54; 6 studies, 2336 participants; high-certainty evidence).

There was no evidence of a difference in asymptomatic intracranial haemorrhage between the IVT and control groups (RR 1.13, 95% CI 1.00 to 1.29; P = 0.06; 6 studies, 2334 participants; high-certainty evidence).

There was probably little to no difference in symptomatic intracranial haemorrhage between the IVT and control groups (RR 1.20, 95% CI 0.84 to 1.70; P = 0.31; 6 studies, 2336 participants; moderate-certainty evidence).

There was a higher rate of successful revascularisation with IVT over control (RR 1.04, 95% CI 1.01 to 1.08; P = 0.008; 6 studies, 2326 participants; high-certainty evidence).

There was a higher rate of complete revascularisation with IVT over control (RR 1.14, 95% CI 1.02 to 1.28; P = 0.02; 5 studies, 2037 participants; high-certainty evidence).

Limitations included: differences in inclusion and exclusion criteria between studies (e.g. age thresholds, pre-existing comorbidities or baseline functional status, time periods, diagnostic imaging, specific vessels); specific endovascular device used; thrombolysis medication and dose; and potential conflict of interest, as multiple study authors reported receiving funding or fees from pharmaceutical companies. For functional independence, assessed as an mRS score < 3 within 90 days, we downgraded the certainty of evidence by one level due to a high I^2 value, indicating that heterogeneity may be substantial for this outcome. For symptomatic intracranial haemorrhage within 90 days, we downgraded the certainty of evidence by one level because the 95% CI included both important benefits and important harms.

Authors' conclusions

The evidence does not currently support a clear benefit or harm for routine intravenous thrombolysis amongst people receiving endovascular thrombectomy.

Amongst participants receiving endovascular thrombectomy, IVT did not demonstrate evidence of a difference in functional independence, excellent functional outcome, mortality, and asymptomatic intracranial haemorrhage, or symptomatic intracranial haemorrhage, when compared with no IVT. However, IVT did result in a higher rate of successful and complete revascularisation when compared with no IVT.

Future research should include more high-quality trials to further evaluate the role of intravenous thrombolysis in people receiving endovascular thrombectomy to provide more robust data and further narrow the confidence intervals. Future research should also identify whether time- and person-specific factors influence the effect of IVT amongst those receiving endovascular thrombectomy.

Funding

None

Registration

Gottlieb M, Carlson JN, Westrick J, Peksa GD. Endovascular thrombectomy with versus without intravascular thrombolysis for acute ischaemic stroke. Cochrane Database of Systematic Reviews. 2024;2:1465-1858.

PLAIN LANGUAGE SUMMARY

For those receiving a procedure to open up vessels after an ischaemic stroke, is clot-busting medicine better than no clot-busting medicine?

Key messages

- For people who received a procedure to open up blood vessels after a stroke, adding a clot-busting medicine:
  - did not make a difference, on average, in their ability to perform daily activities on their own with slight or moderate disability, in the number of deaths, or in bleeding inside the brain with or without symptoms.
  - resulted in a higher flow of blood that could be seen going through the previously blocked blood vessels.

What is acute ischaemic stroke?

In an ischaemic stroke, the blood flow to the brain is decreased by blockage of a blood vessel. If this is not treated quickly, the brain tissue becomes injured, leading to symptoms, such as changes in the ability to speak, move, or walk. In this case, acute means it happened within the past 4.5 hours.

How is acute ischaemic stroke treated?

Treatments for an acute ischaemic stroke include a procedure to open up the blood vessels (endovascular thrombectomy), and clot-busting medicines (intravenous thrombolysis).

What did we want to find out?

We wanted to find out whether giving a clot-busting medicine to people who were receiving an endovascular thrombectomy led to better outcomes than not giving it.

What did we do?

We searched for studies that compared groups of people who received clot-busting medicine to those who did not receive it when they had their endovascular thrombectomy. We compared and summarised the results, and rated our confidence in the evidence, based on factors, such as study methods and sizes.

What did we find?

We found six studies, with a total of 2336 people who just had an ischaemic stroke, and who received a procedure to open up their blood vessels. They were randomised (divided so that everyone had the same chance to receive the medicine) to receive a clot-busting medicine or not receive a clot-busting medicine. The average age was 71 years. There were 1034 women and 1302 men. Both groups had, on average, almost the same level of disability at the beginning of the studies.

People who received a procedure to open up their blood vessels after a stroke and were given a clot-busting medicine did not, on average, do any better than those who did not get the clot-busting medicine, in their ability to perform daily activities on their own with slight or moderate disability, in the number of deaths, or in bleeding inside the brain. However, they did have a higher flow of blood seen going through the blocked blood vessels.

What are the limitations of the evidence?

We are confident that the clot-busting medicine made little or no difference, on average, in moderate disability, the number of deaths, or bleeding inside the brain, without symptoms.

We are also confident that the clot-busting medicine improved the flow of blood that could be seen going through the blocked blood vessels.

We are moderately confident that clot-busting medicine probably made little to no difference, on average, to the ability to perform daily activities on one's own with a slight disability. Our confidence in the evidence is moderate because we had concerns about the wide range of results, and differences between studies.

We are moderately confident that the clot-busting medicine probably made little to no difference in bleeding in the brain, with symptoms. Our confidence in the evidence is only moderate because of our concerns about the wide range of values, which could include a meaningful difference.

How up-to-date is this evidence?

The evidence is up-to-date to November 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Endovascular thrombectomy with intravenous thrombolysis compared to thrombectomy alone for acute ischaemic stroke

Thrombectomy + IVT compared to thrombectomy alone for acute ischaemic stroke

Patient or population: persons with acute ischaemic stroke

Setting: hospital setting with thrombectomy capability

Intervention: thrombectomy + IVT

Comparison: thrombectomy alone

Time point: within 90 days

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty
	Risk with thrombectomy alone	Risk with thrombectomy + IVT			
Functional independence; assessed with mRS < 3	**523** per 1000	**539 per 1000** (481 to 596)	**RR 1.03** (0.92 to 1.14)	2336 (6 RCTs)	⊕⊕⊕○ Moderate[a]
Excellent functional outcome; assessed with mRS < 2	**343** per 1000	**340 per 1000** (316 to 360)	**RR 0.99** (0.92 to 1.05)	2336 (6 RCTs)	⊕⊕⊕⊕ High
Mortality	**160** per 1000	**150 per 1000** (124 to 182)	**RR 0.94** (0.78 to 1.14)	2336 (6 RCTs)	⊕⊕⊕⊕ High
Asymptomatic intracranial haemorrhage	**262** per 1000	**297 per 1000** (262 to 339)	**RR 1.13** (1.00 to 1.29)	2334 (6 RCTs)	⊕⊕⊕⊕ High
Symptomatic intracranial haemorrhage	**47** per 1000	**57 per 1000** (40 to 80)	**RR 1.20** (0.84 to 1.70)	2336 (6 RCTs)	⊕⊕⊕○ Moderate[b]
Successful revascularisation; assessed with TICI grades 2b to 3	**807** per 1000	**840 per 1000** (816 to 872)	**RR 1.04** (1.01 to 1.08)	2326 (6 RCTs)	⊕⊕⊕⊕ High
Complete revascularisation; assessed with: TICI grade 3	**340** per 1000	**387 per 1000** (347 to 435)	**RR 1.14** (1.02 to 1.28)	2037 (5 RCTs)	⊕⊕⊕⊕ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IVT:** intravenous thrombolysis; **mRS:** modified Rankin Scale; **RR:** risk ratio; **TICI:** thrombolysis in cerebral infarction

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Footnotes

[a]Downgraded one level for inconsistency: large I^2 value (I^2 = 67%), indicating heterogeneity may be substantial.

[b]Downgraded one level for imprecision: the 95% CI (0.84 to 1.70) fails to exclude important benefit or harm.

BACKGROUND

Description of the condition

Stroke is a major cause of death and disability worldwide, with over 12 million cases diagnosed each year [1]; it is the second leading cause of death and third leading cause of death and disability [1]. Data suggest that the incidence is expected to increase by 20% between 2012 and 2030 in the USA, while direct annual stroke-related medical costs are expected to increase from USD 71.6 billion to USD 183.1 billion [2].

Acute ischaemic stroke is the most common type of stroke, representing 87% of all strokes [3]. It is typically diagnosed by history and examination, in conjunction with diagnostic imaging, such as magnetic resonance imaging. Acute ischaemic stroke occurs when there is a disruption of blood flow to the brain from a blood clot, which causes damage to the brain tissue, and can result in the loss of specific neurological functions, such as the ability to talk, swallow, or walk. The loss of function can significantly impact quality of life, with research suggesting that quality of life declines significantly after a stroke, even in the absence of subsequent strokes [3].

Description of the intervention and how it might work

Once diagnosed, the interventions for treating acute ischaemic stroke are generally limited to intravenous thrombolysis, endovascular thrombectomy, or both. Intravenous thrombolysis is the injection of a medication to dissolve a blood clot. It is commonly offered to people within the first 4.5 hours of symptom onset, provided there is a significant neurological deficit (loss), and the individual does not meet criteria that would prevent them from receiving this medication [4, 5]. Endovascular thrombectomy is a time-sensitive, minimally invasive surgical procedure to remove a blood clot. It is reserved for people with large vessel occlusions (blockage of larger arteries in the brain), and has been shown to increase the likelihood of survival with a good functional outcome, without increasing the risk of intracranial haemorrhage (bleeding within the brain) or death [6]. Some experts have proposed intravenous thrombolysis prior to endovascular thrombectomy, as a bridging therapy while awaiting endovascular thrombectomy, to increase the likelihood of treatment success, and possibly avoid the need for thrombectomy altogether [7].

Intravenous thrombolysis may have several potential benefits when given in conjunction with endovascular thrombectomy (i.e. before, at the same time as, or immediately after endovascular thrombectomy). Intravenous thrombolysis may lead to successful reperfusion (restoration of blood flow after blockage), removing the need for endovascular thrombectomy [8]. It may change the composition of the clot, and make it more likely to be successfully removed by endovascular thrombectomy [7]. There may also be residual thrombi and new emboli as a result of endovascular thrombectomy, which intravenous thrombolysis may help resolve [7].

However, the addition of intravenous thrombolysis to endovascular thrombectomy has potential risks. First, initiation of intravenous thrombolysis takes time and may delay endovascular intervention if the steps are not taken in parallel [7]. Intravenous thrombolysis may change the composition of the clot, potentially reducing its size and allowing it to migrate to an area that is less accessible or inaccessible for endovascular thrombectomy [7]. Intravenous thrombectomy carries a risk of anaphylaxis (severe allergic reaction) and increases the risk of intracranial haemorrhage [5]. Finally, administration of intravenous thrombolysis may increase resource use and healthcare costs.

Why it is important to do this review

Given the potential benefits and harms of administering intravenous thrombolysis in conjunction with endovascular thrombectomy, there is a need for an up-to-date review to determine the efficacy and safety of this approach compared with endovascular thrombectomy alone. Several randomised controlled trials have been published on this topic, prompting the need for a systematic review to summarise their findings, and evaluate the certainty of the current evidence base.

OBJECTIVES

To assess the effects of receiving endovascular thrombectomy with intravenous thrombolysis versus without intravenous thrombolysis on functional independence (defined as a modified Rankin Scale score < 3) within 90 days, in people with acute ischaemic stroke.

METHODS

We followed the Methodological Expectations of Cochrane Intervention Reviews (MECIR) when conducting the review, and PRISMA 2020 for the reporting [9, 10] Compared with the original protocol, we revised the title and inclusion criteria to narrow the focus to intravenous, rather than intravascular thrombolysis. The rationale for this decision was that intravascular thrombolysis included intra-arterial thrombolysis, which was only performed amongst participants receiving endovascular interventions, and was notably different from intravenous thrombolysis.

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) only. We did not include quasi-randomised studies, cluster-randomised studies, cross-over studies, or non-randomised studies, due to the risk of bias inherent in such designs. We included studies reported in full text or in an abstract only.

Types of participants

We included adults (aged 18 years or older) with acute ischaemic stroke (within 24 hours of onset) who received endovascular thrombectomy in the hospital setting. We included any endovascular thrombectomy techniques (e.g. angiojet aspiration, laser recanalisation, thrombo-aspiration/retrieval devices, mechanical fragmentation of the thrombus, implantation of stents). If subsets of participants were eligible, we planned to contact study authors for information, and include the participants if they were randomised at the level of the subset.

Types of interventions

The intervention consisted of intravenous thrombolysis (e.g. alteplase, tenecteplase) given within 4.5 hours to individuals who received endovascular thrombectomy. The comparator was placebo or no intravenous thrombolysis. We did not plan to modify the analyses to account for co-interventions, as there are no known

co-interventions which would meaningfully impact the outcomes in these trials.

Outcome measures

We included studies that met the inclusion criteria, and assessed at least one of the following outcomes over a time period of up to 90 days. We selected this time period as it is clinically relevant and commonly used for assessment in published studies on this topic. When multiple time points were available, we used the time point closest to 90 days. For functional outcomes, we used the modified Rankin Scale (mRS), which consists of a score from 0 to 6, based on the participant's degree of disability or dependence [11]. We analysed outcomes of both functional independence and excellent functional outcome. Functional independence (mRS score < 3) is defined as 'up to a slight disability', when the participant is unable to carry out all previous activities, but is able to look after their own affairs without assistance. Excellent functional outcome (mRS score < 2) is defined as no disability, or no significant disability despite symptoms, when the participant is able to carry out all usual duties and activities.

Critical outcomes

- Functional independence: mRS score < 3

Important outcomes

- Excellent functional outcome: mRS score < 2
- Mortality
- Asymptomatic intracranial haemorrhage: as defined by the individual studies
- Symptomatic intracranial haemorrhage: as defined by the individual studies
- Successful revascularisation: the proportion of participants with thrombolysis in cerebral infarction (TICI) grades 2b to 3
- Complete revascularisation: the proportion of participants with TICI grade 3 only

Search methods for identification of studies

Electronic searches

A library Research Information Specialist (JW) designed the search strategies for databases included in this review. We searched the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2023, Issue 11) in the Cochrane Library (searched 27 November 2023)
- Cochrane Database of Systematic Reviews (2023, Issue 11) in the Cochrane Library (searched 27 November 2023)
- MEDLINE Ovid (1946 to 27 November 2023)
- Embase (1974 to 27 November 2023)
- Scopus (2004 to 27 November 2023)
- LILACS (Latin American and Caribbean Health Sciences; 1982 to 27 November 2023)
- Google Scholar (27 November 2023)

We did not restrict the search by language of publication, year of publication, location of study (e.g. country), age of participants, or any other limitation. We searched using controlled vocabulary when provided, and used a title/abstract field code restriction on our keywords.

To ensure that no included or eligible studies were the subject of any published concerns, we ran a search on 25 November 2024 in both the Ovid and Scopus databases. Both MeSH terms and keywords were used to locate post-publication amendments, such as errata, letters, corrigenda, and retractions. None of the included or eligible studies had post-publication concerns.

The search strategy for all sources can be found in the appendices (Supplementary material 1).

Searching other resources

We searched the following clinical trial registries for ongoing trials on 27 November 2023.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (https://trialsearch.who.int/)

In addition, we screened reference lists of review articles. We retrieved any additional studies that met the inclusion criteria from these reference lists. We contacted the study authors for additional information where necessary.

Data collection and analysis

Selection of studies

For screening and selection, we transferred the search results to Covidence [12]. Two review authors (MG, JNC) independently screened the titles and abstracts to determine the eligibility of each report identified by the search. We excluded reports that clearly did not satisfy inclusion criteria. We resolved disagreements by consensus, with the adjudication of a third review author (GDP) if needed. The review authors obtained full copies of the remaining reports.

Two review authors (MG, JNC) independently read the full-text reports to select those that met the inclusion criteria. In the event of disagreement, a third review author (GDP) adjudicated them. We did not anonymise the reports before the assessment. We collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We included a PRISMA flow diagram and characteristics of excluded studies table to show the status of identified reports and reasons for exclusion [9]. We included studies in the review regardless of whether they reported outcome data in a 'usable' way.

Data extraction and management

Two review authors (MG, JNC) independently extracted data in duplicate, using a standard piloted form, and checked for agreement. We piloted the form with three studies. In the event of disagreement, a third review author (GDP) adjudicated them. When data were missing or unclear, we contacted the study authors for additional information. We contacted study authors by email a minimum of three times. We collected the characteristics of the included studies in sufficient detail to populate characteristics of included studies tables. We converted data found in studies to a format appropriate for meta-analysis. One review author (GDP) entered the data into Review Manager (RevMan [13]), and it was checked by a second review author (MG). We extracted the following information.

Methods

- Study date
- Study design
- Study country
- Study duration
- Follow-up duration
- Publication type

Participants

- Total number of participants in each group
- Inclusion criteria
- Exclusion criteria
- Mean or median age
- Sex or gender distribution
- Baseline stroke severity in each group (defined by the National Institutes of Health Stroke Scale (NIHSS))
- Type of endovascular thrombectomy performed

Interventions

- Type, dose, and timing of intervention
- Control group (i.e. placebo or no intravascular thrombolysis)
- Concomitant medications or interventions

Outcomes

- mRS within 90 days in each group
  - Functional independence: defined as mRS score < 3
  - Excellent functional outcome: defined as mRS score < 2
- Mortality within 90 days in each group
- Asymptomatic intracranial haemorrhage within 90 days in each group
  - As defined by the individual studies
- Symptomatic intracranial haemorrhage within 90 days in each group
  - As defined by the individual studies
- Degree of revascularisation within 90 days, defined by the thrombolysis in cerebral infarction (TICI) grade in each group
  - Successful revascularisation, defined as the proportion of participants with TICI grades 2b to 3
  - Complete revascularisation, defined as the proportion of participants with TICI grade 3 only

Other

- Funding source
- Author conflicts of interest
- Number of participants lost to follow-up
- Deviations from intended interventions

Risk of bias assessment in included studies

Two review authors (MG, JNC) independently assessed the risk of bias for each outcome, using the criteria outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* [14], and the RoB 2 tool [15]. We resolved any disagreements by discussion. A third review author (GDP) adjudicated any disagreements not resolved by discussion. We used the RoB 2 Excel tool provided by Cochrane to assist with assessments. We analysed studies according to assignment (i.e. by intention-to-treat).

We assessed the following biases for each outcome:

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

We assessed each potential source of bias based on answers to the RoB 2 signalling questions [15]. We summarised our risk of bias judgements for each outcome across different studies for each of the domains listed, where the overall risk of bias for the result was the least favourable assessment across the domains of bias. We illustrated the risk of bias graphically, and added risk of bias information to our forest plots, where possible. Our overall risk of bias assessment informed our GRADE assessment.

Measures of treatment effect

We used the risk ratio (RR) to measure treatment effects for dichotomous data. All of our outcomes were dichotomous. We reported treatment effects with 95% confidence intervals (CIs), and used forest plots to present the data. We converted data from sample sizes and percentages, as needed, for meta-analysis.

Unit of analysis issues

When RCTs included more than two groups, we planned to combine data for the thrombolysis arms (e.g. alteplase and tenecteplase). However, no RCTs included more than two groups. We combined data for endovascular thrombectomy techniques (e.g. angiojet aspiration, laser recanalisation, thrombo-aspiration/retrieval devices, mechanical fragmentation of the thrombus, implantation of stents) to create a single pair-wise comparison.

For RCTs with repeated measures, we planned to use the outcome measure closest to 90 days for the evaluation of functional independence and excellent functional outcome.

Dealing with missing data

We contacted investigators to verify missing study characteristics and missing numerical outcome data. We used intention-to-treat (ITT) data to minimise the impact of unknown information due to study participant attrition. We calculated missing data from sample sizes and percentages, as needed, for meta-analysis. We planned to perform sensitivity analyses excluding studies in which bias due to missing outcome data was deemed high.

Reporting bias assessment

We planned to create and assess a funnel plot for the primary outcome if we included more than 10 studies in the review. We planned to use a formal statistical test for asymmetry [16]. We intended to assess small study effects and non-reporting biases as possible explanations for asymmetry. We planned to consider additional possible sources of asymmetry in funnel plots of true heterogeneity, artefactual causes, and chance [16]. However, because the review included only six studies, a funnel plot and statistical testing were inappropriate.

Synthesis methods

Meta-analysis of numerical data

We pooled outcome data using the random-effects model, as described by DerSimonian and Laird [17]. We performed meta-analysis using the Mantel-Haenszel method incorporated in Review Manager (Supplementary material 6, [13]). We chose to use the random-effects model regardless of the assessment of statistical heterogeneity, in order to address clinical differences in the studies that may be unexplained through our investigation of statistical heterogeneity. In addition, the random-effects method will give similar results to the fixed-effect method when heterogeneity is low.

Synthesis using other methods

When a meta-analysis could not be undertaken, we planned appropriate visual display and presentation of the data, using forest plots without summary estimates. We intended to follow Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* in our approach to presenting findings using other methods [18].

We assessed the statistical heterogeneity of pooled studies by visual inspection of forest plots to consider the direction and magnitude of effects. We used the Chi^2 test and I^2 statistic. For the Chi^2 test, we considered $P < 0.10$ to indicate statistically significant heterogeneity (i.e. variation in effect estimates beyond that expected by chance). We used the I^2 statistic to classify heterogeneity as follows [19]:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of the I^2 statistic depends on the magnitude and direction of effects, and the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for the I^2 statistic). Uncertainty about the value of the I^2 statistic is substantial when the number of studies is small.

We planned to assess clinical heterogeneity related to clinical diversity in region, participant characteristics (baseline stroke severity and location of large vessel occlusion), and methodological diversity with interventions (type of endovascular thrombectomy and thrombolytic medication administered). We summarised these details in the characteristics of included studies tables, and planned to conduct subgroup analyses when sufficient studies existed (Investigation of heterogeneity and subgroup analysis). However, because the review included only six studies, subgroup analyses were inappropriate.

Investigation of heterogeneity and subgroup analysis

We planned to use the following subgroup analyses to explore sources of heterogeneity for the primary outcome measure.

- Stroke severity: mild to moderate (NIHSS ≤ 15) versus severe to very severe (NIHSS > 15)
- Location of large vessel occlusion: middle cerebral artery (inclusive of M1 and M2 branches) versus non-middle cerebral artery
- Type of endovascular thrombectomy: stent retriever versus aspiration retriever
- Thrombolytic medication administered: alteplase versus tenecteplase

We chose stroke severity because more severe strokes at baseline may adversely impact functional outcome. We planned to explore the location of large vessel occlusion, the type of endovascular thrombectomy used, and the type of thrombolytic medication administered, because these factors may alter the effect of the intervention on the functional outcome. While currently there are no comparative data to demonstrate differences between these for endovascular thrombectomy with versus without intravascular thrombolysis, it is feasible they may affect the results and may merit future research.

We planned to only compare subgroups if sufficient studies (10 or more) per subgroup were available for evaluation. We planned to compare differences across subgroups using the significance test outlined by Borenstein and Higgins [20]. Participants were unlikely to be randomised into subgroups; therefore, we planned to treat our subgroup analyses as observational comparisons, because they were not based on randomised comparisons. If confidence intervals did not overlap, we planned to consider this an indication of statistical significance. However, because the review included only six studies, subgroup analyses were inappropriate.

Equity-related assessment

This was not conducted because it was not planned a priori in the protocol. Equity-related assessments were not planned for this review, as data were not available to analyse equity-based outcomes on our preliminary searches, and the review question is less aligned with an equity focus.

Sensitivity analysis

We planned to perform a sensitivity analysis to examine the impact of the risk of bias in the studies by excluding studies we deemed to be at overall high risk of bias. We also planned to perform a sensitivity analysis excluding studies for which we deemed the risk of bias due to missing outcome data to be high. For the primary outcome, we planned to assess mRS within 90 days, but also intended to perform a sensitivity analysis for studies that evaluated mRS early (within 30 days). We planned to consider, for sensitivity analysis, whether studies used a placebo or no intervention for the comparator group.

Certainty of the evidence assessment

Assessment of the certainty of the evidence

Two review authors (MG, GDP) independently judged the certainty of the body of evidence for the outcomes. To rank the certainty of the evidence, we adopted the GRADE system using GRADEpro GDT software [21], and the guidelines provided in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* [22].

The GRADE approach considers five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The GRADE approach specifies four possible levels of certainty for a body of evidence for a given outcome: high, moderate, low, and very low. We used the following definitions for each grade of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

According to the GRADE system, RCTs provide high-certainty evidence, which can be downgraded for important limitations [23]. We decreased the GRADE rating if we identified any of the following:

- serious or very serious study design limitations;
- serious or very serious inconsistency of results;
- serious or very serious uncertainty about directness;
- serious or very serious imprecision;
- the probability of reporting bias.

We justified our decisions to downgrade the certainty of the evidence in footnotes, and provided comments to aid readers' understanding of our judgements.

Summary of findings table

We included a single summary of findings table to present the main findings of our 'Thrombectomy plus intravenous thrombolysis compared to thrombectomy alone or plus placebo' comparison in a transparent and simple tabular format. We formulated the summary of findings table using GRADEpro GDT software [21]. We included key information for our seven outcomes about the certainty of the evidence, the size of effects of the interventions examined, and the sum of available data.

Consumer involvement

This was not conducted because it was not planned a priori in the protocol. Consumers were not involved in this review due to limited resources, although we did use core outcome sets for the review's outcomes, which were developed with consumer involvement.

RESULTS

Description of studies

Results of the search

Our search identified a total of 9382 records (Figure 1). After removing duplicates, we reviewed 6264 unique records. Of those, 6245 were not relevant to the review, so we excluded them during the initial screening stage. We reviewed 19 full-text articles and excluded 13 records for specific reasons (Supplementary material 3). We selected six studies for this review (Supplementary material 2). We did not identify any ongoing trials.

Figure 1.

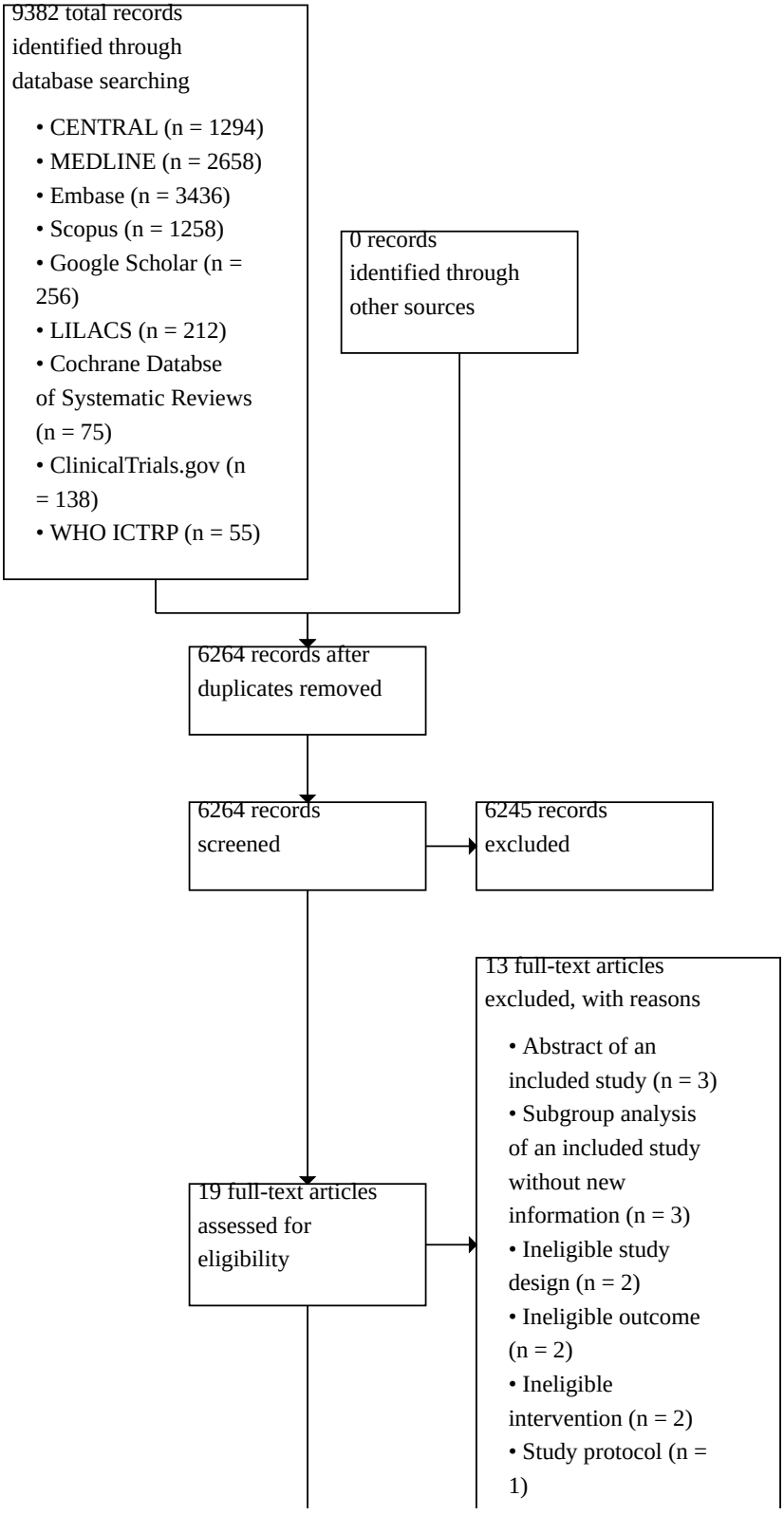
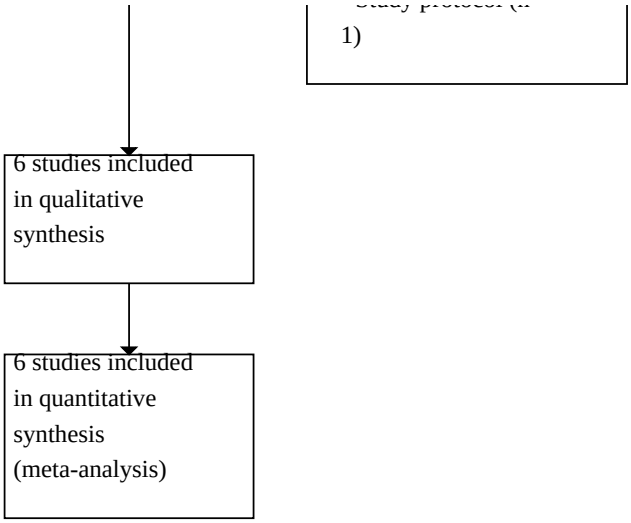


Figure 1. (Continued)



Included studies

Table 1 is a summary of included studies and syntheses. For the quantitative synthesis, we included six studies with 2336 participants (Supplementary material 5). Of these, 1166 were assigned to the control group and 1170 were assigned to the intravenous thrombolysis group. The mean age was 71 years. There were 1034 (44.3%) women and 1302 (55.7%) men in the studies. The mean National Institutes of Health Stroke Scale (NIHSS) score for the control group was 17, while the mean score for the intervention group was 16.

Studies were conducted in multiple countries, including China (Mitchell 2022 [24]; Yang 2020A [25]; Zi 2021A [26]), France (Fischer 2022 [27]; LeCouffe 2021 [28]), Belgium (LeCouffe 2021), Austria (Fischer 2022), Australia (Mitchell 2022), Canada (Fischer 2022), Finland (Fischer 2022), Germany (Fischer 2022), Japan (Suzuki 2021 [29]), the Netherlands (LeCouffe 2021), New Zealand (Mitchell 2022), United Kingdom (Fischer 2022), Spain (Fischer 2022), Switzerland (Fischer 2022), and Vietnam (Mitchell 2022).

Five studies included participants if the vessel occlusion involved the middle cerebral artery or intracranial internal carotid artery (Fischer 2022; LeCouffe 2021; Suzuki 2021; Yang 2020A; Zi 2021A), whereas one study included the middle cerebral artery, intracranial internal carotid artery, or basilar artery (Mitchell 2022). Alteplase 0.9 mg/kg was used in four studies (Fischer 2022; LeCouffe 2021; Yang 2020A; Zi 2021A), alteplase 0.6 mg/kg was used in one study (Suzuki 2021), and one study used either alteplase 0.9 mg/kg or tenecteplase 0.25 mg/kg (Mitchell 2022). All studies used the absence of intravenous thrombolysis as their control group; no studies used a placebo.

Excluded studies

We excluded 16 studies based on a full-text review (Supplementary material 3). Of these, three studies were excluded as they were abstracts of already included studies without new information, three were subgroup analyses without new information, two had an ineligible study design, two did not have eligible outcomes, two had an ineligible intervention, and one was a study protocol of an already included study.

Risk of bias in included studies

All six studies were deemed at overall low risk of bias for each of the outcomes, as discussed below. The risk of bias judgements are presented in Supplementary material 4.

Functional independence (modified Rankin Scale (mRS) score < 3) within 90 days

We assessed all six studies at low risk for bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and overall bias.

Excellent functional outcome (mRS < 2) within 90 days

We assessed all six studies at low risk for bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and overall bias.

Mortality within 90 days

We assessed all six studies at low risk for bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and overall bias.

Asymptomatic intracranial haemorrhage within 90 days

We assessed all six studies at low risk for bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and overall bias.

Symptomatic intracranial haemorrhage within 90 days

We assessed all six studies at low risk for bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and overall bias.

Successful revascularisation within 90 days (thrombolysis in cerebral infarction (TICI) grades 2b to 3)

We assessed all six studies at low risk for bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and overall bias.

Complete revascularisation within 90 days (TICI grade 3 only)

We assessed all six studies at low risk for bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and overall bias.

Complete responses to signalling questions related to the risk of bias assessments are available upon request to the corresponding author.

Synthesis of results

Endovascular thrombectomy with intravascular thrombolysis (IVT) versus thrombectomy alone

Critical outcome

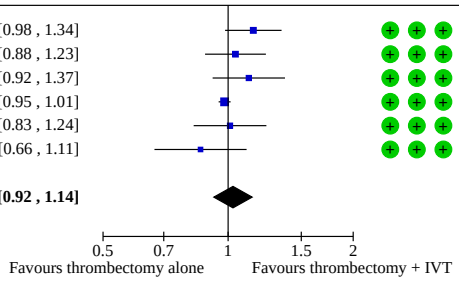
Functional independence: mRS score < 3, within 90 days

All six studies reported this outcome (Fischer 2022; LeCouffe 2021; Mitchell 2022; Suzuki 2021; Yang 2020A; Zi 2021A). There was probably little to no difference in functional independence between the IVT and control groups (RR 1.03, 95% CI 0.92 to 1.14; P = 0.62; 6 studies, 2336 participants; moderate-certainty evidence; Analysis 1.1; Figure 2; Summary of findings 1; Supplementary material 5).

Figure 2.

Study or Subgroup	Thrombectomy + IVT Events	Total	Thrombectomy alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Fischer 2022	135	207	114	201	17.5%	1.15 [0.98 , 1.34]	+ + + + + +
LeCouffe 2021	136	266	134	273	16.5%	1.04 [0.88 , 1.23]	+ + + + + +
Mitchell 2022	88	147	79	148	14.0%	1.12 [0.92 , 1.37]	+ + + + + +
Suzuki 2021	101	103	101	101	27.4%	0.98 [0.95 , 1.01]	+ + + + + +
Yang 2020A	121	329	119	327	14.0%	1.01 [0.83 , 1.24]	+ + + + + +
Zi 2021A	55	118	63	116	10.7%	0.86 [0.66 , 1.11]	+ + + + + +
Total (Wald[a])		**1170**		**1166**	**100.0%**	**1.03 [0.92 , 1.14]**	
Total events:	636		610				

Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.01; Chi² = 15.37, df = 5 (P = 0.009); I² = 67%



Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

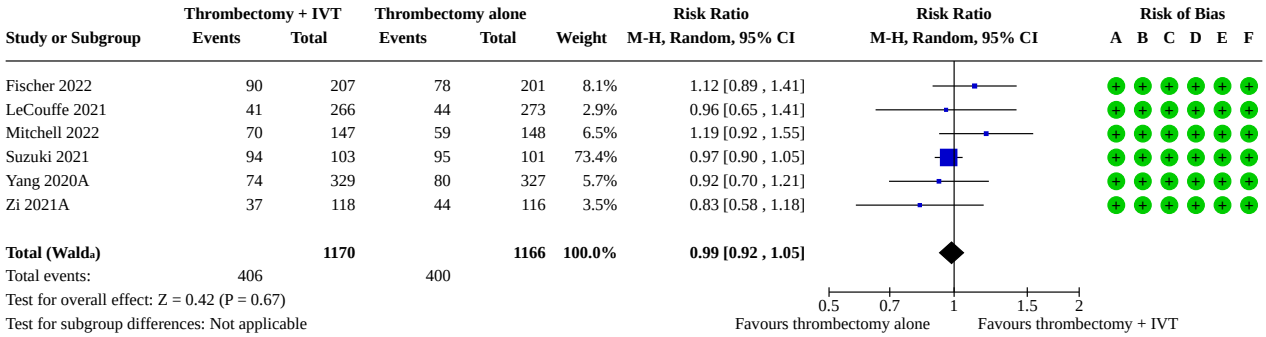
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Important outcomes

Excellent functional outcome: mRS score < 2, within 90 days

All six studies reported this outcome (Fischer 2022; LeCouffe 2021; Mitchell 2022; Suzuki 2021; Yang 2020A; Zi 2021A). There was no evidence that thrombectomy with IVT affected an excellent functional outcome (RR 0.99, 95% CI 0.92 to 1.05; P = 0.67; 6 studies, 2336 participants; high-certainly evidence; Analysis 1.2; Figure 3; Summary of findings 1; Supplementary material 5).

Figure 3.



Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 4.95, df = 5 (P = 0.42); I² = 0%

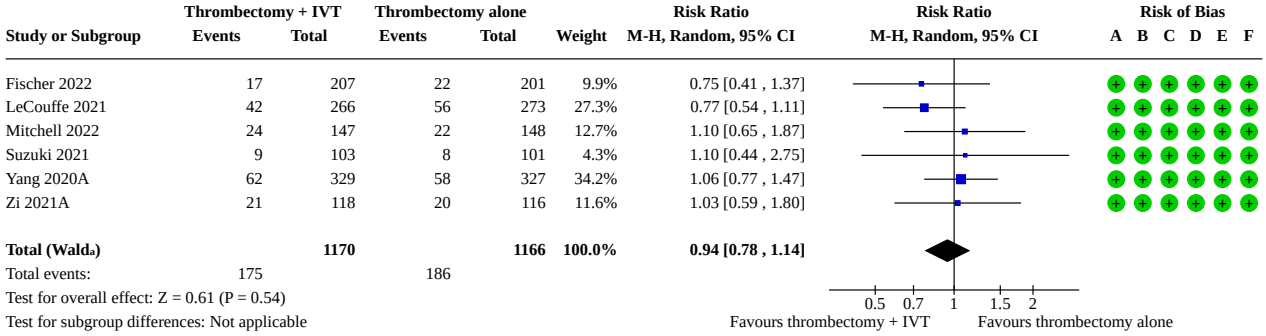
Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Mortality, within 90 days

All six studies reported this outcome (Fischer 2022; LeCouffe 2021; Mitchell 2022; Suzuki 2021; Yang 2020A; Zi 2021A). There was no evidence of a difference in mortality between groups (RR 0.94, 95% CI 0.78 to 1.14; P = 0.54; 6 studies, 2336 participants; high-certainly evidence; Analysis 1.3; Figure 4; Summary of findings 1; Supplementary material 5).

Figure 4.



Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 2.81, df = 5 (P = 0.73); I² = 0%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Asymptomatic intracranial haemorrhage, within 90 days

All six studies reported this outcome (Fischer 2022; LeCouffe 2021; Mitchell 2022; Suzuki 2021; Yang 2020A; Zi 2021A). Two studies reported haemorrhage follow-up at five to seven days (LeCouffe 2021; Yang 2020A), one study reported follow-up at 48 hours (Zi 2021A), two studies reported follow-up at 36 hours (Mitchell 2022; Suzuki 2021), and one study reported follow-up at 24 hours (Fischer 2022). There was no evidence of a difference in the

risk of an asymptomatic haemorrhage between groups (RR 1.13, 95% CI 1.00 to 1.29; P = 0.06; 6 studies, 2336 participants; high-certainly evidence; Analysis 1.4; Figure 5; Summary of findings 1; Supplementary material 5).

Figure 5.

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

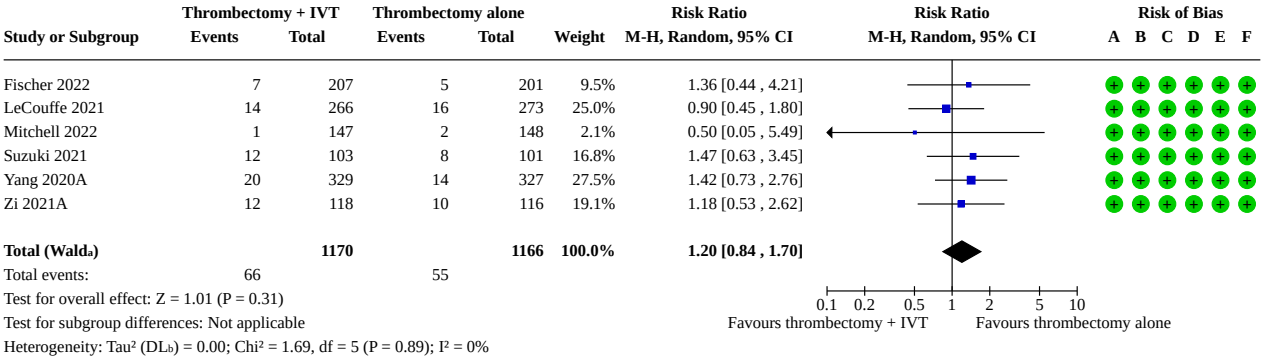
(E) Bias in selection of the reported result

(F) Overall bias

Symptomatic intracranial haemorrhage, within 90 days

All six studies reported this outcome (Fischer 2022; LeCouffe 2021; Mitchell 2022; Suzuki 2021; Yang 2020A; Zi 2021A). Two studies reported haemorrhage follow-up at five to seven days (LeCouffe 2021; Yang 2020A), one study reported follow-up at 48 hours (Zi 2021A), two studies reported follow-up at 36 hours (Mitchell 2022; Suzuki 2021), and one study reported follow-up at 24 hours (Fischer 2022). There was probably little to no difference in the risk of symptomatic haemorrhage between groups (RR 1.20, 95% CI 0.84 to 1.70; P = 0.31; 6 studies, 2336 participants; moderate-certainty evidence; Analysis 1.5; Figure 6; Summary of findings 1; Supplementary material 5).

Figure 6.



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

Successful revascularisation, within 90 days: TICI grades 2b to 3

All six studies reported this outcome (Fischer 2022; LeCouffe 2021; Mitchell 2022; Suzuki 2021; Yang 2020A; Zi 2021A). Thrombectomy with IVT was better for successful revascularisation than thrombectomy alone (RR 1.04, 95% CI 1.01 to 1.08; P = 0.008; 6 studies, 2336 participants; high-certainly evidence; Analysis 1.6; Figure 7; Summary of findings 1; Supplementary material 5).

Figure 7.

Study or Subgroup	Thrombectomy + IVT Events	Total	Thrombectomy alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fischer 2022	199	207	182	201	36.2%	1.06 [1.01 , 1.12]
LeCouffe 2021	196	266	192	273	9.0%	1.05 [0.94 , 1.16]
Mitchell 2022	130	146	127	143	15.0%	1.00 [0.92 , 1.09]
Suzuki 2021	96	103	91	101	14.4%	1.03 [0.95 , 1.12]
Yang 2020A	267	329	243	327	14.7%	1.09 [1.01 , 1.19]
Zi 2021A	102	117	100	113	10.7%	0.99 [0.89 , 1.08]
Total (Wald[a])		**1168**		**1158**	**100.0%**	**1.04 [1.01 , 1.08]**
Total events:	990		935			

Risk Ratio M-H, Random, 95% CI

Risk of Bias A B C D E F

0.5 0.7 1 1.5 2

Favours thrombectomy alone Favours thrombectomy + IVT

Test for overall effect: Z = 2.64 (P = 0.008)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 4.01, df = 5 (P = 0.55); I² = 0%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Complete revascularisation, within 90 days: TICI grade 3 only

Five studies measured this outcome (Fischer 2022; LeCouffe 2021; Suzuki 2021; Yang 2020A; Zi 2021A). Thrombectomy with IVT was better for complete revascularisation than thrombectomy alone (RR 1.14, 95% CI 1.02 to 1.28; P = 0.02; 5 studies, 2037 participants; high-certainty evidence; Analysis 1.7; Figure 8; Summary of findings 1; Supplementary material 5).

Figure 8.

Study or Subgroup	Thrombectomy + IVT Events	Total	Thrombectomy alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fischer 2022	75	207	67	201	18.5%	1.09 [0.83 , 1.42]
LeCouffe 2021	120	266	100	273	31.2%	1.23 [1.00 , 1.51]
Suzuki 2021	45	103	40	101	12.3%	1.10 [0.80 , 1.53]
Yang 2020A	107	329	94	327	24.5%	1.13 [0.90 , 1.43]
Zi 2021A	50	117	44	113	13.4%	1.10 [0.80 , 1.50]
Total (Wald[a])		**1022**		**1015**	**100.0%**	**1.14 [1.02 , 1.28]**
Total events:	397		345			

Risk Ratio M-H, Random, 95% CI

Risk of Bias A B C D E F

0.2 0.5 1 2 5

Favours thrombectomy alone Favours thrombectomy + IVT

Test for overall effect: Z = 2.32 (P = 0.02)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.77, df = 4 (P = 0.94); I² = 0%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Subgroup analyses

We did not perform any subgroup analyses, because study-level data did not allow us to delineate results according to our preplanned subgroups.

Sensitivity analyses

We did not perform any sensitivity analyses because we judged all the included studies at low risk of bias; all the studies evaluated mRS within 90 days; and all the studies used thrombectomy alone for the comparator group.

DISCUSSION

Summary of main results

In this systematic review, we identified six studies that evaluated endovascular thrombectomy with versus without intravenous thrombolysis. Overall, intravenous thrombolysis did not demonstrate evidence of a difference in functional independence, excellent functional outcome, mortality, asymptomatic intracranial haemorrhage, or symptomatic intracranial haemorrhage. However, intravenous thrombolysis did lead to increased rates of successful and complete revascularisation on visualised blood flow assessment.

Limitations of the evidence included in the review

The evidence in this review was sufficient to adequately address most of the objectives of this review question. However, this review was limited by differences in inclusion and exclusion criteria between studies, which included age thresholds, pre-existing comorbidities, baseline functional status, time periods, diagnostic imaging, and specific vessels. There were also differences in the specific endovascular device used. While most studies used a single medication and dose (alteplase 0.9 mg/kg), one study used a lower dose (Suzuki 2021), and a second study used either alteplase 0.9 mg/kg or tenecteplase 0.25 mg/kg (Mitchell 2022). There were no studies that exclusively assessed tenecteplase, which has demonstrated superiority over alteplase in the treatment of acute ischaemic stroke [30]. All the studies were non-inferiority studies, and were not powered for superiority. While none of the studies were directly funded by pharmaceutical companies, multiple study authors did report receiving funding or fees from pharmaceutical companies, which could present a potential conflict of interest. For the outcome of functional independence, assessed within 90 days, by an mRS < 3, certainty of evidence was reduced due to a large I^2 value, indicating heterogeneity may be substantial for this outcome. For the outcome of symptomatic intracranial haemorrhage, assessed within 90 days, certainty of evidence was reduced because the 95% confidence interval failed to exclude important benefit or important harm.

Limitations of the review processes

While we conducted a comprehensive search across multiple databases, using an expansive search strategy, it is possible that relevant studies may have been missed due to publication bias or reporting bias. We sought to reduce this risk by consulting experts and reviewing clinical trial registries for missed studies. In addition, our search was limited by the available data. We sought to reduce this risk by reviewing all published papers on a given trial, and contacting study authors for additional information. As such, we were able to obtain additional unpublished information on all the included studies. Nonetheless, we were limited by data collected and available to the review authors, which limited our ability to collect some variables, such as concomitant medications or interventions. We were limited by the total number of studies, and insufficient trials available to conduct the planned subgroup analyses. Finally, we were limited by the total participant numbers. Further trials may lead to differences in select findings.

Agreements and disagreements with other studies or reviews

This review has several notable similarities and differences with prior reviews. A 2021 review included three trials with 1092 participants, and reported no evidence of a difference in functional independence, excellent functional outcome, mortality, successful reperfusion, or symptomatic intracranial haemorrhage [31]. Our review adds to this by including twice the number of trials and participants, as well as including additional outcomes of asymptomatic intracranial haemorrhage and complete reperfusion. We identified similar findings, except intravenous thrombolysis increased reperfusion in our review. A 2022 review included four trials with 1622 participants, and reported no evidence of a difference in functional outcomes, successful reperfusion, intracranial haemorrhage, or mortality [32]. Our review adds to this by increasing the number of trials and participants, while also identifying that intravenous thrombolysis increased reperfusion. Another 2022 review included four trials with 1633 participants, and reported no evidence of a difference in functional independence, excellent functional outcome, successful reperfusion, symptomatic intracranial haemorrhage, or mortality [33]. The group did identify a difference in total intracranial haemorrhages. Our review builds upon this by increasing the number of studies and participants. We found no evidence of a difference in symptomatic or asymptomatic intracranial haemorrhage, but a higher rate of successful and complete revascularisation in the intravenous thrombolysis group. A separate 2022 review included the same six studies as we did, and found similar results for functional independence, excellent functional outcome, mortality, and symptomatic intracranial haemorrhage [34]. Our review also included asymptomatic intracranial haemorrhage and reperfusion outcomes. A 2023 review included seven trials with 2317 participants, and reported no evidence of a difference in successful recanalisation, functional independence, symptomatic intracranial haemorrhage, or mortality [35]. Notably, their review included both randomised and non-randomised trials, which could have introduced bias in the results. Our review differs from theirs. We only included randomised trials, had a larger number of total participants, and identified differences in recanalisation rates. Finally, a 2023 individual participant-level meta-analysis included six studies with 2313 participants, and reported no evidence of a difference in symptomatic intracranial haemorrhage or mortality, but a higher rate of successful recanalisation and a higher rate of total intracranial haemorrhages [36]. A subgroup analysis by the same authors assessed the impact of the time to intravenous thrombolysis, and identified a time-dependent effect, with better functional outcomes occurring within the initial 140 minutes [37]. While we were unable to perform an individual participant-level meta-analysis based on the time to thrombolysis, our study

builds upon this by reporting comparable results for functional independence and excellent functional outcome.

AUTHORS' CONCLUSIONS

Implications for practice

Based upon this review, the evidence does not currently support a clear benefit or harm for routine intravenous thrombolysis amongst people with acute ischaemic stroke receiving endovascular thrombectomy.

The addition of intravenous thrombolysis did not result in evidence of a difference in functional independence, excellent functional outcome, mortality, asymptomatic intracranial haemorrhage, or symptomatic intracranial haemorrhage. While there was a difference in recanalisation with intravenous thrombolysis, this did not demonstrate a meaningful difference in patient-oriented outcomes.

The potential benefits of incorporating this into practice include improved reperfusion, which may result in subtle improvements in neurologic symptoms not identified through the mRS. While the data suggest no evidence of a difference in functional outcomes, an improvement in specific neurologic symptoms not identified through the current data may still have a patient-oriented improvement in quality of life.

The potential harms of incorporating this into practice include increased rates of haemorrhage. While our study did not identify evidence of a difference in asymptomatic or symptomatic intracranial haemorrhage, other reviews have reported increased rates of total intracranial haemorrhage with intravenous thrombolysis [33, 36]. The use of intravenous thrombolysis may also delay the time to endovascular thrombectomy [35]. Intravenous thrombolysis also requires dedicated clinical resources, which can reduce total capacity to care for other people. Finally, increasing use of intravenous thrombolysis can further contribute to rising healthcare costs.

Implications for research

Based upon the data from our review, there are several areas in need of further research. More high-quality trials are needed to further evaluate the role of intravenous thrombolysis in people receiving endovascular thrombectomy, to provide more robust data and further narrow the confidence intervals. These trials should better elucidate the influence of medication, dosing, timing, and specific endovascular intervention. Future research should also identify whether time- and patient-specific factors influence the effect of intravenous thrombolysis amongst those receiving endovascular thrombectomy. For example, one recent study suggested there may be a time-dependent role for intravenous thrombolysis [37]. Finally, future research should identify the effect of intravenous thrombolysis on a broader range of neurologic symptoms beyond functional status alone.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD015721.

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Risk of bias

Supplementary material 5 Analyses

Supplementary material 6 Data package

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

• Sign-off Editor (final editorial decision): Peter Langhorne, University of Glasgow;

• Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Sara Hales-Brittain, Central Editorial Service;

• Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Addie-Ann Smyth, Cochrane Central Editorial Service;

• Copy Editor (copy editing and production): Victoria Pennick, Cochrane Central Production Service;

• Peer-reviewers (provided comments and recommended an editorial decision): Prof Bruce Campbell, Department of Medicine and Neurology, Royal Melbourne Hospital, University of Melbourne, Parkville, Australia (clinical/content review); Diana Frost PPi member (consumer review); Jo-Ana Chase, Cochrane Evidence Production and Methods Directorate (methods review); Jo Platt, Central Editorial Information Specialist (search review). An additional peer reviewer provided clinical/content peer review but chose not to be publicly acknowledged.

Contributions of authors

Conception and design of the review: MG, JNC, JW, GDP

Co-ordination of the review: MG

Search and selection of studies for inclusion in the review: MG, JNC, JW, GDP

Collection of data for the review: MG, JNC, GDP

Assessment of the risk of bias in the included studies: MG, JNC, GDP

Analysis of data: GDP

Assessment of the certainty in the body of evidence: MG, GDP

Interpretation of data: MG, JNC, GDP

Writing and revising the review: MG, JNC, JW, GDP

Declarations of interest

MG: none known. MG is an emergency medicine physician who cares for patients with acute stroke in the acute care setting.

JW: none known. JW is a research librarian at an academic medical centre.

JNC: none known. JNC is an emergency medicine physician who cares for patients with acute stroke in the acute care setting. JNC has received funding from the American Heart Association for intubation research.

GDP: none known. GDP is a clinical pharmacist who works in the Emergency Department.

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- None, Other

  Nothing to declare

History

Protocol first published: Issue 2, 2024

Registration and protocol

Gottlieb M, Carlson JN, Westrick J, Peksa GD. Endovascular thrombectomy with versus without intravascular thrombolysis for acute ischaemic stroke. Cochrane Database of Systematic Reviews. 2024;2:1465-1858.

Data, code and other materials

As part of the published Cochrane Review, the following are made available for download for users of the Cochrane Library: full search strategies for each database; full citations of each unique report for all studies included; ongoing or waiting classification, or excluded at the full text screen, in the final review; study data, including study information, study arms, and study results or test data; consensus risk of bias assessments; and analysis data, including overall estimates and settings, subgroup estimates, and individual data rows. Appropriate permissions have been obtained for such use. Analyses and data management were conducted within Cochrane's authoring tool, RevMan, using the inbuilt computation methods. Template data extraction forms from Microsoft Excel are available from the authors on reasonable request.

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ADDITIONAL TABLES

Table 1. Overview of included studies and syntheses

Study ID	Country of conduct	Study design	Intervention characteristics (control / intervention)	Population (mean or median age / % female)	Sample size: control / intervention	Baseline NIHSS control / intervention	Outcomes with available data	Specific outcome measures and time points	Method of synthesis
Fischer 2022	Austria, Canada, Finland, France, Germany, United Kingdom, Spain, and Switzerland	RCT	No intravenous thrombolysis / alteplase 0.9 mg/kg	72 / 51.2	408: 201 / 207	17 / 17	• Functional independence • Excellent functional outcome • Mortality • Asymptomatic or symptomatic ICH • Successful or complete revascularisation	mRS at 90 days Mortality at 90 days ICH at 24 hours	MA
LeCouffe 2021	Netherlands, Belgium, and France	RCT	No intravenous thrombolysis / alteplase 0.9 mg/kg	71 / 43.4	539: 273 / 266	16 / 16	• Functional independence • Excellent functional outcome • Mortality • Asymptomatic or symptomatic ICH • Successful or complete revascularisation	mRS at 90 days Mortality at 90 days ICH at 5-7 days	MA
Mitchell 2022	Australia, China, New Zealand, and Vietnam	RCT	No intravenous thrombolysis / alteplase 0.9 mg/kg or tenecteplase 0.25 mg/kg	69 / 43.3	295: 148 / 147	15 / 15	• Functional independence • Excellent functional outcome • Mortality • Asymptomatic or symptomatic ICH • Successful revascularisation	mRS at 90 days Mortality at 90 days ICH at 36 hours	MA
Suzuki 2021	Japan	RCT	No intravenous thrombolysis / alteplase 0.6 mg/kg	75 / 37.3	204: 101 / 103	19 / 17	• Functional independence • Excellent functional outcome • Mortality • Asymptomatic or symptomatic ICH • Successful or complete revascularisation	mRS at 90 days Mortality at 90 days ICH at 36 hours	MA

Table 1. Overview of included studies and syntheses *(Continued)*

Yang 2020A	China	RCT	No intravenous thrombolysis / alteplase 0.9 mg/kg	69 / 43.6	656: 327 / 329	17 / 17	• Functional independence • Excellent functional outcome • Mortality • Asymptomatic or symptomatic ICH • Successful or complete revascularisation	mRS at 90 days Mortality at 90 days ICH at 5 to 7 days	MA
Zi 2021A	China	RCT	No intravenous thrombolysis / alteplase 0.9 mg/kg	70 / 43.6	234: 116 / 118	16 / 16	• Functional independence • Excellent functional outcome • Mortality • Asymptomatic or symptomatic ICH • Successful or complete revascularisation	mRS at 90 days Mortality at 90 days ICH at 48 hours	MA

ICH: intracranial haemorrhage; **MA:** meta-analysis; **mRS**: modified Rankin Scale; **NIHSS**: National Institute of Health Stroke Scale; **RCT**: randomized controlled trial

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; *Endovascular Procedures [adverse effects] [methods]; *Fibrinolytic Agents [administration & dosage] [adverse effects]; Intracranial Hemorrhages [epidemiology]; *Ischemic Stroke [mortality] [therapy]; Randomized Controlled Trials as Topic; *Thrombectomy [adverse effects] [methods]; *Thrombolytic Therapy [adverse effects] [methods]

MeSH check words

Aged; Humans