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Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke (Review)

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[Intervention Review]

Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke

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ABSTRACT

Background

Most disabling strokes are due to a blockage of a large artery in the brain by a blood clot. Prompt removal of the clot with intra-arterial thrombolytic drugs or mechanical devices, or both, can restore blood flow before major brain damage has occurred, leading to improved recovery. However, these so-called endovascular interventions can cause bleeding in the brain. This is a review of randomised controlled trials of endovascular thrombectomy or intra-arterial thrombolysis, or both, for acute ischaemic stroke.

Objectives

To assess whether endovascular thrombectomy or intra-arterial interventions, or both, plus medical treatment are superior to medical treatment alone in people with acute ischaemic stroke.

Search methods

We searched the Trials Registers of the Cochrane Stroke Group and Cochrane Vascular Group (last searched 1 September 2020), CENTRAL (the Cochrane Library, 1 September 2020), MEDLINE (May 2010 to 1 September 2020), and Embase (May 2010 to 1 September 2020). We also searched trials registers, screened reference lists, and contacted researchers.

Selection criteria

Randomised controlled trials (RCTs) of any endovascular intervention plus medical treatment compared with medical treatment alone in people with definite ischaemic stroke.

Data collection and analysis

Two review authors (MBR and MJ) applied the inclusion criteria, extracted data, and assessed trial quality. Two review authors (MBR and HL) assessed risk of bias, and the certainty of the evidence using GRADE. We obtained both published and unpublished data if available. Our primary outcome was favourable functional outcome at the end of the scheduled follow-up period, defined as a modified Rankin Scale score of 0 to 2. Eighteen trials (i.e. all but one included trial) reported their outcome at 90 days. Secondary outcomes were death from all causes at in the acute phase and by the end of follow-up, symptomatic intracranial haemorrhage in the acute phase and by the end of follow-up, neurological status at the end of follow-up, and degree of recanalisation.

Main results

We included 19 studies with a total of 3793 participants. The majority of participants had large artery occlusion in the anterior circulation, and were treated within six hours of symptom onset with endovascular thrombectomy. Treatment increased the chance of achieving a good functional outcome, defined as a modified Rankin Scale score of 0 to 2: risk ratio (RR) 1.50 (95% confidence interval (CI) 1.37 to 1.63; 3715 participants, 18 RCTs; high-certainty evidence). Treatment also reduced the risk of death at end of follow-up: RR 0.85 (95% CI 0.75 to 0.97; 3793 participants, 19 RCTs; high-certainty evidence) without increasing the risk of symptomatic intracranial haemorrhage in the acute phase: RR 1.46 (95% CI 0.91 to 2.36; 1559 participants, 6 RCTs; high-certainty evidence) or by end of follow-up: RR 1.05 (95% CI 0.72 to 1.52; 1752 participants, 10 RCTs; high-certainty evidence); however, the wide confidence intervals preclude any firm conclusion. Neurological recovery to National Institutes of Health Stroke Scale (NIHSS) score 0 to 1 and degree of recanalisation rates were better in the treatment group: RR 2.03 (95% CI 1.21 to 3.40; 334 participants, 3 RCTs; moderate-certainty evidence) and RR 8.25 (95% CI 1.63 to 41.90; 198 participants, 2 RCTs; moderate-certainty evidence), respectively.

Authors' conclusions

In individuals with acute ischaemic stroke due to large artery occlusion in the anterior circulation, endovascular thrombectomy can increase the chance of survival with a good functional outcome without increasing the risk of intracerebral haemorrhage or death.

PLAIN LANGUAGE SUMMARY

Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke

Review question

This review addressed whether endovascular thrombectomy (removal of a blood clot in a blood vessel using a mechanical device) or intra-arterial thrombolysis (injecting clot-dissolving drugs directly into the clot), or both, provide better outcomes than standard treatment alone in stroke caused by a blocked blood vessel.

Background

The majority of disabling strokes are due to a blockage of a large blood vessel by a blood clot in the brain. Such strokes lead to brain tissue damage because of oxygen deprivation. An ischaemic stroke is a stroke where the restriction of blood flow causes damage and death to the surrounding tissue due to oxygen shortage. For these patients, the most intuitive means of treatment is removal of the blockage by either injecting clot-dissolving drugs directly into the clot or removal of the blood clot using a mechanical device, or both. Prompt treatment can restore blood flow before major brain damage has occurred, leading to a good recovery. However, these treatments can also cause bleeding in the brain, which can result in poorer outcomes. We searched for randomised controlled trials (studies in which participants are assigned to one of two or more treatment groups using a random method) of both endovascular mechanical thrombectomy and intra-arterial thrombolysis to establish whether they are safe and effective treatments for stroke caused by a blocked blood vessel.

Search date

1 September 2020

Study characteristics

Randomised controlled trials of endovascular thrombectomy or intra-arterial thrombolysis, or both, plus routine medical treatment compared with routine medical treatment alone in people with a definite acute ischaemic stroke.

Study funding sources

No funding sources.

Key results

We found 19 trials involving a total of 3793 participants. Treatment with endovascular thrombectomy can improve patients' chance of survival with the ability to function well without increasing the risk of bleeding in the brain or death. It is still unclear what the optimal time window is within which treatment is beneficial and whether treatment is effective in the posterior (supplying the rear part of the brain) circulation. There is also a need to study whether a strategy of primary endovascular thrombectomy or intra-arterial thrombolysis, or both, is superior to a strategy where intravenous (injected into the vein) clot-dissolving treatment is provided first in a local centre followed by transfer of selected patients to hospitals able to perform mechanical thrombectomy or intra-arterial thrombolysis, or both.

Certainty of the evidence

We judged the available trials to be at low or unclear risk of bias, and so overall the evidence is reported to be of high certainty.

Summary of findings 1. Endovascular thrombectomy interventions compared to standard therapy for acute ischaemic stroke

Endovascular thrombectomy interventions compared to standard therapy for acute ischaemic stroke

Patient or population: acute ischaemic stroke
Setting: hospital
Intervention: endovascular thrombectomy or intra-arterial interventions, or both
Comparison: standard therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with routine medical treatment	Risk with endovascular thrombectomy interventions			
Favourable functional outcome at the end of follow-up (primary outcome: mRS score 0 to 2) Follow-up: 90 days[a]	290 per 1000	435 per 1000 (397 to 475)	RR 1.50 (1.37 to 1.63)	3715 (18 RCTs)	⊕⊕⊕⊕ High[b]
Death from all causes at the end of follow-up Follow-up: 90 days[a]	207 per 1000	176 per 1000 (153 to 203)	RR 0.85 (0.75 to 0.97)	3793 (19 RCTs)	⊕⊕⊕⊕ High[b]
Symptomatic intracranial haemorrhage at the end of follow-up (NINDS) Follow-up: 90 days[a]	58 per 1000	58 per 1000 (37 to 88)	RR 1.05 (0.72 to 1.52)	1752 (10 RCTs)	⊕⊕⊕⊕ High[b]
Neurological status at the end of follow-up (NIHSS) Follow-up: 90 days[a]	123 per 1000	250 per 1000 (149 to 418)	RR 2.03 (1.21 to 3.40)	334 (3 RCTs)	⊕⊕⊕⊖ Moderate[b,c]
Degree of recanalisation (TIMI grade) Follow-up: End of endovascular procedure	16 per 1000	129 per 1000 (25 to 655)	RR 8.25 (1.63 to 41.90)	198 (2 RCTs)	⊕⊕⊕⊖ Moderate[b,c]

*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; **mRS:** modified Rankin Scale; **NINDS:** National Institute of Neurological Disorders and Stroke; **RCT:** randomised controlled trial; **RR:** risk ratio

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.

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[a]All trials had 90 days follow-up with the exception of one trial of 16 patients (AUST 2005).
[b]Only one of these RCTs could be blinded for surgeons or participants due to the nature of the intervention.
[c]Downgraded for imprecision (wide confidence interval)

BACKGROUND

Acute ischaemic stroke is a major cause of death and disability worldwide (Warlow 2003). The usual mechanism is a thrombotic occlusion of a cerebral artery; intravenous thrombolytic treatment with recombinant tissue plasminogen activator (rt-PA) within 4.5 hours of stroke onset reduces disability (Wardlaw 2009), and is the routine recanalisation treatment. The rapidly developing field of interventional radiology currently offers a variety of alternative approaches to recanalisation in acute ischaemic stroke. This is a review of randomised controlled trials of endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke (O'Rourke 2010).

Description of the condition

An ischaemic stroke is caused by the disruption of blood flow due to a blood clot, which results in brain tissue damage and loss of function. Ischaemic stroke constitutes approximately 80% to 85% of all strokes.

Description of the intervention

Endovascular thrombectomy and intra-arterial techniques are recanalisation therapies where the blood clot is either removed using a mechanical device, most often stent retrievers; or thrombolytic medication is injected by intra-arterial means directly to the blood clot. We included all the following techniques.

- Angiojet aspiration
- Laser recanalisation
- Thromboaspiration (retrieval devices)
- Angioplasty
- Mechanical fragmentation of the thrombus
- Implantation of stents
- Intra-arterial thrombolysis
- Intra-arterial sonothrombolysis

How the intervention might work

The goal of endovascular thrombectomy and intra-arterial interventions is to remove or dissolve the blood clot causing the stroke symptoms, either by using a mechanical device or, in some cases, by injecting thrombolytic drugs, such as urokinase or alteplase, directly to the embolus, or by a combination of both techniques. If recanalisation is achieved, the patient's affected brain tissue can recover, and if done in time and without complications, the patient's functional outcome can be significantly improved.

Why it is important to do this review

An up-to-date review on endovascular thrombectomy and intra-arterial thrombolysis for acute ischaemic stroke is highly warranted and will clarify the efficacy and safety of these relatively new acute treatment modalities for acute ischaemic stroke, which is in rapid development and gaining considerable clinical significance in acute stroke care. Several new publications in this field are included in this updated and highly relevant review.

OBJECTIVES

To assess whether endovascular thrombectomy or intra-arterial interventions, or both, plus medical treatment are superior to medical treatment alone in people with acute ischaemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing endovascular thrombectomy and intra-arterial interventions plus medical treatment to medical treatment alone in people with definite acute ischaemic stroke. We excluded cluster randomised trials.

Types of participants

People with a definite acute ischaemic stroke (a computed tomography (CT) or magnetic resonance imaging (MRI) must have excluded cerebral haemorrhage).

Types of interventions

All endovascular thrombectomy and intra-arterial techniques aimed at revascularisation in acute ischaemic stroke, including but not limited to:

- angiojet aspiration;
- laser recanalisation;
- thromboaspiration (retrieval devices);
- angioplasty;
- mechanical fragmentation of the thrombus;
- implantation of stents;
- intra-arterial thrombolysis;
- intra-arterial sonothrombolysis.

All types of medical treatment could be given in addition to the endovascular thrombectomy and intra-arterial techniques.

Type of comparison therapy

The comparison therapy was routine medical treatment. Intravenous thrombolytic treatment was permissible only when the same intravenous thrombolytic treatment was also given to the intervention group.

Types of outcome measures

Primary outcomes

Favourable functional outcome at the end of the scheduled follow-up period defined as a modified Rankin Scale (mRS) score of 0 to 2. Given that some prefer a definition of 'favourable outcome' as a score of 0 to 1 (NINDS 1995), we also sought data on the number of participants in each individual mRS category. If the mRS score was not reported, we used the trial's definition of functional outcome. Eighteen of the included trials (i.e. all but one trial: AUST 2005) reported their outcome at 90 days.

Secondary outcomes

- Death from all causes, both:
  - during the acute phase, i.e. first seven to 10 days; and
  - at the end of scheduled follow-up.

- Symptomatic intracranial haemorrhage within the acute phase (non-fatal or fatal) and at the end of follow-up. We defined symptomatic intracranial haemorrhage according to both the National Institute of Neurological Disorders and Stroke (NINDS) study (NINDS 1995), and the European Cooperative Acute Stroke Study (ECASS) criteria (Hacke 1995). When symptomatic intracranial haemorrhage was not reported according to these criteria, we used the trial's definition.
- Neurological status at the end of follow-up. We defined favourable neurological outcome as National Institutes of Health Stroke Scale (NIHSS) score 0 to 1.
- Degree of recanalisation, according to Higashida 2003, and using the Thrombolysis In Myocardial Infarction (TIMI) grade (Khatri 2005) or the Thrombolysis In Cerebral Infarction (TICI) grade.
- Major extracranial haemorrhage in the acute phase.

Search methods for identification of studies

See the methods for the Cochrane Stroke Group Specialised Register. We searched for trials in all languages and arranged for translation of trial reports where necessary.

Electronic searches

We searched the Cochrane Stroke Group Specialised Register (1 September 2020) and the Trials Register of Cochrane Vascular Group (last searched 1 September 2020). In addition, we updated the searches in the following electronic databases. (We adapted the MEDLINE search strategy for the other databases.)

- MEDLINE Ovid (from May 2010 to 1 September 2020) (Appendix 1).
- Embase Ovid (from May 2010 to 1 September 2020) (Appendix 2).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 8) in the Cochrane Library (searched 1 September 2020). (Appendix 3)
- Science Citation Index (from 1980 to 1 September 2020). (Appendix 4)

We also searched the following ongoing trials registers (last searched 1 September 2020).

- Stroke Trials Registry (www.strokecenter.org/trials).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov). (Appendix 5)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en).

Searching other resources

In an attempt to identify further published, unpublished, ongoing or planned trials, we screened reference lists of relevant trials and contacted professional organisations in neuroradiology and interventional radiology, and authors and researchers active in the field.

Data collection and analysis

Selection of studies

Randomised controlled trials comparing endovascular thrombectomy and intra-arterial interventions plus medical treatment versus medical treatment alone in people with acute ischaemic stroke. Two review authors (MBR and MJ) screened the titles and abstracts of references identified by the searches. We obtained full-paper copies of those trial reports which appeared to be eligible for inclusion based on the title and abstract. Two review authors (MBR and MJ) then assessed these for inclusion in the review. Any disagreements between the authors were resolved by discussion, with input from a third review author (HL) if needed. When a trial was excluded, we kept a record of both the report and the reason for exclusion.

Data extraction and management

Two review authors (MBR and MJ) independently extracted data from the report of each eligible trial on a specially designed data extraction form. The review authors were not blinded to journal or institution. Any disagreements between the authors were resolved by discussion, with input from a third review author (HL) if needed. We extracted the following information from each report.

- Diagnostic criteria used for acute ischaemic stroke, including whether magnetic resonance imaging (MRI) diffusion/perfusion mismatch, computed tomography (CT) angiography, or CT perfusion were used to identify eligible patients.
- Time interval from onset to randomisation.
- Time of groin puncture or initiation of intra-arterial treatment.
- Numbers of participants in each treatment group with outcome events.
- Modality of endovascular thrombectomy or intra-arterial intervention used.
- Precise form of comparison therapy used.
- Data on subgroups (NIHSS score, age, time to treatment, early ischaemic changes on CT according to the Alberta Stroke Program Early CT Score (ASPECTS), use of intravenous thrombolytic medication, and sex).

One review author (MBR) entered the data into Review Manager 5 software (Review Manager 2020). These data were checked by another review author (HL) against the hard copy data extraction forms to correct and clarify data entry errors. When any relevant data were missing from the available publications, we contacted the principal investigators or industrial sponsors concerned.

Assessment of risk of bias in included studies

Two review authors (MBR and HL) performed risk of bias assessment of all the included studies using Cochrane's risk of bias tool.

Quality assessment

Two review authors (MBR and HL) independently performed quality assessment of reports of eligible trials, resolving any disagreements by discussion. We used the following criteria to assess the quality of reports of eligible trials, according to Section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- adequate sequence generation;
- allocation concealment;
- blinding: in trials of endovascular thrombectomy it is not possible to blind either the participants or those administering the interventions. However, outcome assessors can be blinded. We defined blinding as 'yes', 'no', or 'unclear' as it pertained to blinding of outcome assessors;

- incomplete outcome data addressed: we considered intention-to-treat analysis (ITT) adequate when:
  * participants were analysed in the groups to which they had been randomised irrespective of the treatment they received; and
  * when the numbers of participants lost to follow-up and the associated reasons were reported.
- free of selective reporting;
- free of other bias.

We used the above criteria to construct a risk of bias table for each eligible trial, as outlined in Section 8.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

We expressed the treatment effects of dichotomous outcomes as risk ratios with 95% confidence intervals (CI). We did not plan to include continuous outcomes.

Unit of analysis issues

The unit of analysis was the participant with acute ischaemic stroke. We excluded crossover trials; due to the nature of the disease and intervention, crossover trials are not possible.

Dealing with missing data

We contacted study authors for missing data. Where possible, ITT analysis was applied. In reporting adverse events, we assumed the 'worst case' to avoid under-reporting.

Assessment of heterogeneity

We identified and measured statistical and clinical heterogeneity as recommended in Section 10.10.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We estimated heterogeneity between trials' results using the I^2 statistic (Higgins 2021).

We defined thresholds for interpreting heterogeneity (I^2) as follows:

- 0% to 30%: no heterogeneity;
- 30% to 50%: moderate heterogeneity;
- 50% to 80%: substantial heterogeneity;
- 80% to 100%: considerable heterogeneity.

The evaluation of heterogeneity was not based on I^2 alone, as the importance of consistency depends on several factors, but rather included an overall evaluation of the data.

Assessment of reporting biases

We undertook extensive literature searching without restrictions on publication date or language in order to limit reporting bias. We used study protocols and trial registrations to assess studies for selective reporting.

Data synthesis

We analysed the data using Review Manager 5 software (Review Manager 2020). Two review authors (MBR and HL) conducted the data analysis. The appropriate statistical analysis was a binary logistic regression. We selected the Mantel-Haenszel method.

We derived risk ratios and 95% CI for each study. We combined the results of the included studies for each outcome where appropriate. We used a fixed-effect model for pooled data and considered not pooling data if we encountered considerable heterogeneity (I^2 value of 80% or more) across studies. We performed subgroup analyses using the methodology described by Deeks and colleagues (Deeks 2001), as recommended in Section 10.11.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses and investigation of heterogeneity (via meta-regression) a priori on the following characteristics.

- Age
- Sex
- Stroke severity
- Early ischaemic changes on CT according ASPECTS
- Mean time to groin puncture or initiation of intra-arterial treatment
- Intravenous thrombolytic medication
- Intra-arterial intervention
- Localisation of cerebral artery occlusion
- Localisation of occlusion

After reviewing the articles, we amended the subgroups to include:

- intra-arterial treatment with and without mechanical thrombectomy;
- penumbra imaging in selecting patients to treatment.

We defined subgroups by age (younger and older participants, using trial definition); sex; stroke severity (according to the NIHSS score, using each trial's cutoff for severe stroke); presence of large infarction on CT (according to ASPECTS, using each trial's cutoff for large infarction), and use of intravenous thrombolytic medication. We compared trials where the mean or median time between stroke onset and initiation of intra-arterial treatment was shorter (< 250 minutes), medium (250 to 300 minutes), or longer (> 300 minutes). We compared trials that included patients with proximal occlusion only and trials of patients with both proximal and non-proximal occlusion. We compared trials where a majority of participants were treated with no mechanical device; trials where a majority of participants were treated with first-generation mechanical devices (i.e. Merci and Penumbra systems); and trials where a majority of participants were treated with stent retrievers. We compared trials that included intra-arterial treatments without mechanical thrombectomy, trials that included both intra-arterial treatments with and without mechanical thrombectomy, and trials that included patients treated with mechanical thrombectomy alone. We also compared trials that used and did not use penumbra imaging for selecting patients to treatment.

Sensitivity analysis

We conducted sensitivity analysis to compare trials included in the previous version of the review and trials identified in the current review. We also compared trials that included all planned participants versus trials that were stopped early. The sensitivity

analysis only examined the primary outcome (mRS 0 to 2, or mRS 0 to 1 if data were not available for mRS 0 to 2).

We conducted a sensitivity analysis by using the random-effects meta analytic estimate on the primary outcome.

Summary of findings and assessment of the certainty of the evidence

We used GRADE when creating the summary of findings table. We summarised the findings in Summary of findings 1 using the GRADE approach as described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We included the following outcomes in the summary of findings table.

- Favourable functional outcome at the end of follow-up
- Death from all causes in the acute phase and at the end of follow-up
- Symptomatic intracranial haemorrhage in the acute phase and at the end of follow-up
- Neurological status at end of follow-up
- Degree of recanalisation

We planned to downgrade the certainty of evidence based on the five GRADE domains (study limitations, imprecision, inconsistency, indirectness, and publication bias) where required and to justify all decisions to downgrade the certainty of evidence.

RESULTS

Description of studies

We included 19 studies involving a total of 3793 participants randomised to either endovascular thrombectomy or intra-arterial interventions, or a combination of these two endovascular treatments, or control (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). This review update includes 15 new RCTs. The previous version included four trials with 350 participants (AUST 2005; MELT 2007; PROACT 1 1998; PROACT 2 1999). There was no statistically significant heterogeneity between the trials included in this review, therefore we deemed a fixed-effect meta-analysis to be appropriate. A total of 20 participants were lost to follow-up across all 19 studies.

Types and severities of strokes

Three studies included participants with middle cerebral artery territory strokes (MELT 2007; PROACT 1 1998; PROACT 2 1999). AUST 2005 and BEST 2019 included participants with posterior circulation strokes. MR RESCUE 2013 included participants with large-vessel, anterior circulation strokes. EASI 2017, IMS III 2013, and THRACE 2016 included participants with both anterior and posterior circulation strokes. THERAPY 2016 included participants with large vessel ischaemic stroke because of a thrombus length of over 8 mm in the anterior circulation. Eight trials included participants with proximal artery occlusion strokes in the anterior circulation (BEST 2019; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; PISTE 2016; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015). DAWN 2018 and DEFUSE 2018 included participants with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery. DAWN 2018 included participants in the extended time window from six up to 24 hours after last known to be well. DEFUSE 2018 included participants in the extended time window from six to 16 hours after last known to be well. See Characteristics of included studies table.

Age and gender of participants

One study included participants aged 18 to 75 years (MELT 2007). Eight studies included participants aged 18 to 80/85 years (AUST 2005; IMS III 2013; MR RESCUE 2013; PROACT 1 1998; PROACT 2 1999; REVASCAT 2015; THERAPY 2016; THRACE 2016). Seven studies included participants from age 18 years without any upper age limit (BEST 2019; DAWN 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; RESILIENT 2020). One study included participants aged 18 to 90 years (DEFUSE 2018).

Mean ages of participants were as follows.

- 64 years (AUST 2005; PROACT 2 1999).
- 65 years (MR CLEAN 2015; MR RESCUE 2013; SWIFT PRIME 2015).
- 66 years (REVASCAT 2015).
- 67 years (MELT 2007; PROACT 1 1998).
- 69 years (EXTEND-IA 2015; IMS III 2013).

The median age of participants in ESCAPE 2015 was 70 years. There was no age imbalance between the intervention and control groups in any of the trials.

Of participants in all 19 included studies, 1093 of 2052 (53%) in the intervention group were men and 941 of 1761 (53%) in the control group were men, so overall there was no significant sex imbalance. There were gender imbalances in six studies (AUST 2005; BEST 2019; PROACT 1 1998; PROACT 2 1999; SWIFT PRIME 2015; THERAPY 2016).

Medical history of participants

For information on the medical backgrounds of participants, see Characteristics of included studies. There were small imbalances for diabetes mellitus in PROACT 2 1999, congestive heart failure in MR RESCUE 2013, and coronary heart disease in IMS III 2013. In eight studies conventional vascular risk factors were well balanced amongst the treatment and control groups (AUST 2005; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MR CLEAN 2015; PISTE 2016; REVASCAT 2015; SWIFT PRIME 2015).

Stroke mechanism

The predominant mechanism of stroke in the included studies was classified as cardioembolism, followed by carotid atheroembolism and unknown mechanism. Lacunar infarcts were not excluded. The proportion of cardioembolic strokes ranged from around 50% in EXTEND-IA 2015 to around 85% in MELT 2007. Fourteen studies did not provide data on stroke mechanism (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; IMS III 2013; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016).

Findings on CT or MRI at randomisation

In PROACT 1 1998 and PROACT 2 1999, most participants had early ischaemic changes on CT, and a minority of participants in these two studies (8%) had ischaemic changes comprising more than one-third of the middle cerebral artery territory. Patients were not excluded from AUST 2005 on the basis of baseline ischaemic CT abnormalities, and in MELT 2007 patients with CT abnormalities

consistent with subtle early ischaemia in the insular cortex, frontal and temporal opercula, or lenticular nuclei were included.

In MR RESCUE 2013, participants were randomised based on the presence or absence of penumbra on CT or MRI. In MR CLEAN 2015, patients were included if a proximal arterial occlusion in the anterior cerebral circulation was confirmed on CT angiography, MRI angiography, or digital subtraction angiography. In ESCAPE 2015, patients were included if an occluded proximal occlusion was observed on CT angiography. Patients with large early ischaemic changes on plain CT (defined as ASPECTS ≤ 5) were excluded. In EXTEND-IA 2015, patients were included if CT angiography showed occluded internal carotid or middle cerebral artery, and there was evidence of ischaemic penumbra on CT perfusion. In SWIFT PRIME 2015, patients were included if CT angiography showed occlusion of the internal carotid or first segment of the middle cerebral artery, and there was evidence of an ischaemic penumbra on CT perfusion. In REVASCAT 2015, patients with large infarction cores (defined as ASPECTS < 7 on CT or < 6 on MRI) were excluded. In IMS III 2013, plain CT and neurological deficits were used to include patients who had an 80% likelihood of proximal occlusion strokes. The trial was amended after 284 participants were randomised to allow the use of CT angiography to identify patients with proximal occlusion strokes. In PISTE 2016, patients were enrolled if CT or MR angiography identified occlusion of the internal carotid, M1 or single proximal M2. In DEFUSE 2018, patients were included if CT perfusion or MRI diffusion and perfusion scans showed an initial infarct volume (ischaemic core) of less than 70 mL, a ratio of volume of ischaemic tissue to initial infarct volume of 1.8 or more, and an absolute volume of potentially reversible ischaemia (penumbra) of 15 mL or more. In THERAPY 2016, CT angiography was required to confirm intracranial occlusion and to rule out tandem cervical occlusion that would prevent thrombectomy without treatment. Enhanced thin-section CT scan was also used to demonstrate over 8-millimetre clot length. However, advanced perfusion imaging selection or multiphase CT or CT angiography was not required. In DAWN 2018, patients were eligible for inclusion in the trial if they had evidence of occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both, on CT angiography or magnetic resonance angiography. In THRACE 2016, occlusions had to be confirmed by CT or magnetic resonance angiography. In EASI 2017, all suspected or proven occlusions of the M1 or M2 segments of the middle cerebral artery, supraclinoid internal carotid artery, or basilar artery were included. Vascular imaging was not mandated in the protocol. In BEST 2019, patients were eligible for inclusion if they had occlusion of the basilar artery confirmed by CT angiography, MRI, or digital subtraction angiography. Patients with occlusion of the distal intracranial vertebral artery (V4 segment) resulting in no flow to the basilar artery were also included. No evidence of intracranial haemorrhage, significant cerebellar mass effect, acute hydrocephalus, or extensive bilateral brainstem ischaemia should be found on CT or MRI. In RESILIENT 2020, patients were eligible for inclusion in the study if they had an occlusion involving the intracranial internal carotid artery, the first segment of the middle cerebral artery (M1), or both. The main imaging exclusion criteria were evidence of recent intracranial haemorrhage; the presence of a large infarct, as defined by ASPECTS < 6 on CT or < 5 on diffusion weighted MRI; and the complete absence of leptomeningeal collaterals on CT angiography. If CT or MRI perfusion was performed, participants had to have a baseline infarct volume of less than 70 mL, a ratio of volume of ischaemic tissue to baseline infarct volume of 1.8 or more, and an absolute volume of potentially reversible ischaemia (penumbra) of 15 mL or more.

Time to randomisation

The protocol-defined time between onset of stroke and inclusion in the trial varied from three to 24 hours. One trial included participants up to three hours after stroke onset (IMS III 2013); two trials included participants up to 4.5 hours after stroke onset (EXTEND-IA 2015; THERAPY 2016); two trials included participants up to five hours after stroke onset (EASI 2017; THRACE 2016); six trials included participants up to six hours after stroke onset (MELT 2007; MR CLEAN 2015; PISTE 2016; PROACT 1 1998; PROACT 2 1999; SWIFT PRIME 2015); four trials included participants up to eight hours after stroke onset (BEST 2019; MR RESCUE 2013; RESILIENT 2020; REVASCAT 2015); one trial included participants up to 12 hours after stroke onset (ESCAPE 2015); one trial included participants from six to 16 hours after last to be known well (DEFUSE 2018); and two trials included participants up to 24 hours after stroke onset (AUST 2005; DAWN 2018).

The actual times to randomisation or start of therapy were variably reported. Time to randomisation was not reported in PROACT 1 1998. The time to actual delivery of endovascular thrombectomy (not start of procedure) in PROACT 1 1998 was a median 5.4 hours for the treatment group and 5.7 hours for the control group. In PROACT 2 1999, the time to randomisation was a median 4.7 hours in the treatment group and 5.1 hours in the control group. In AUST 2005, the onset to treatment time was a mean 11.8 hours in the treatment group and 12.5 hours in the control group. In MELT 2007, the onset to randomisation time was a mean 3.3 hours in the treatment group and 3.4 hours in the control group. In MR RESCUE 2013, the onset to randomisation time was 5.3 hours in the treatment group and 5.8 hours in the control group. In SWIFT PRIME 2015, the onset to randomisation time was three hours in both groups. In MR CLEAN 2015, the onset to randomisation time was 3.4 hours in both groups. In ESCAPE 2015 and REVASCAT 2015, the onset to randomisation time was 2.8 hours in both groups. The onset to randomisation time was not reported in EXTEND-IA 2015 and IMS III 2013. In IMS III 2013, the time to actual delivery of endovascular thrombectomy or intravenous thrombolytic therapy (not start of procedure) was 4.2 hours in the treatment group. In EXTEND-IA 2015, the median time from stroke onset to groin puncture was 3.5 hours in the treatment group. In DAWN 2018, the median time interval between the time that the participant was last known to be well and randomisation was 12.2 hours in the treatment group. In THERAPY 2016, stroke onset to randomisation time was reported as 181 minutes. In EASI 2017, time from stroke onset to randomisation was not reported, but the authors reported that 50% of participants in the treatment group were randomised within three hours of stroke onset. In THRACE 2016, time from stroke onset to randomisation was a median 168 minutes in the treatment group. In DEFUSE 2018, median time from stroke onset to randomisation was 10 hours and 53 minutes in the treatment group.

Participants in nine studies, ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016, were randomised earlier than participants in six studies (AUST 2005; DAWN 2018; DEFUSE 2018; MR RESCUE 2013; PROACT 1 1998; PROACT 2 1999).

Method of recanalisation

Four trials tested only intra-arterial interventions with either the drug urokinase or pro-urokinase to achieve thrombolysis (AUST 2005; MELT 2007; PROACT 1 1998; PROACT 2 1999). There were differences between these trials in dose, form, and method of drug delivery. See Characteristics of included studies table. No participants in these four studies were given intravenous thrombolytic treatment (AUST 2005; MELT 2007; PROACT 1 1998; PROACT 2 1999).

Five trials approved the use of both mechanical thrombectomy and intra-arterial interventions (BEST 2019; IMS III 2013; MR CLEAN 2015; MR RESCUE 2013; THRACE 2016). In MR CLEAN 2015, intra-arterial treatment consisted of arterial catheterisation with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, or mechanical thrombectomy was performed, or both, with the method used left to the discretion of the local interventionist. In this study either alteplase at a maximum dose of 90 mg or urokinase 1,200,000 international units (IU) was used for intra-arterial thrombolysis in the case of intra-arterial treatment. In IMS III 2013, the approach used was chosen by the local neurointerventionist and encompassed receiving mechanical thrombectomy or endovascular delivery of tissue plasminogen activator (tPA) by means of microcatheter. In BEST 2019 and MR RESCUE 2013, intra-arterial interventions were approved as rescue therapy. In THRACE 2016, intra-arterial interventions of maximum 0.3 mg/kg were approved in cases of persistent distal occlusions.

Mechanical clot disruption was prohibited by the protocol in PROACT 1 1998 and did not occur in AUST 2005. The protocols of eight trials permitted use of mechanical clot disruption, either using a guidewire or by employing stents or other devices (ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; REVASCAT 2015; SWIFT PRIME 2015). In IMS III 2013 and MR RESCUE 2013, participants were primarily treated with first-generation mechanical devices (i.e. Merci and Penumbra systems). The majority of participants were treated with stent retrievers in 10 trials (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; PISTE 2016; REVASCAT 2015; SWIFT PRIME 2015). In DEFUSE 2018, any US Food and Drug Administration (FDA)-approved thrombectomy device was allowed to perform thrombectomy. In DAWN 2018, thrombectomy was performed with the use of the Trevo device, a retrievable self-expanding stent. No other devices or intra-arterial pharmacological agents were allowed. In THRACE 2016, any device on the list from the trial's regularly updated list that was also approved by the ethics committee and the French National Agency for the Safety of Medicines and Health Products could be chosen. The following devices were used: Merci, Penumbra, Catch, and Solitaire. In EASI 2017, thrombectomy was performed using an approved device according to local practice. In THERAPY 2016, aspiration thrombectomy was performed using the Penumbra system and included the Separator 3D after December 2012, and the larger-bore ACE aspiration catheter after August 2013. In RESILIENT 2020, thrombectomy was performed with the Solitaire FR stent retriever or Penumbra aspiration system. Angioplasty and stenting of the cervical internal carotid artery could be performed if necessary. Standard medical care included the use of alteplase, following the guidelines of the Brazilian Stroke Society and the American Heart Association. In BEST 2019, participants received intravenous alteplase if they met the criteria for intravenous thrombolysis within 4.5 hours of stroke symptom onset as per existing guidelines. Mechanical thrombectomy was performed with stent retriever (preferred choice) or thrombo-aspiration devices. Ten trials used only endovascular mechanical thrombectomy and no intra-arterial thrombolysis (DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; PISTE 2016; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016).

A total of 445 participants (89%) from MR CLEAN 2015, 44 participants (37%) from MR RESCUE 2013, 18 participants (10%) from DEFUSE 2018, 46 participants (60%) from EASI 2017, 150 participants (73%) from REVASCAT 2015, 18 participants (9%) from DAWN 2018, and 238 participants (75%) from EXTEND-IA 2015 were given intravenous thrombolytic treatment before randomisation. The inclusion criteria of six studies specified that all participants should be given intravenous thrombolytic treatment as a bridging to intra-arterial treatment (ESCAPE 2015; IMS III 2013; PISTE 2016; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016).

Concomitant use of antithrombotic treatment

The protocols for concomitant antithrombotic therapy varied amongst trials. There may have been an imbalance in the use of antithrombotic therapy in PROACT 1 1998, where safety concerns prompted an alteration of the concomitant antithrombotic regimen during the trial. Similarly, the MELT 2007 protocol specified that heparin, warfarin, and aspirin should not be given for 24 hours in the treatment group. In DAWN 2018, participants who had not received intravenous alteplase could receive therapy with antiplatelet agents after 24 hours postrandomisation. Standard medical care was provided in accordance with local guidelines. Ten studies did not report differences between the intervention and the control group in the use of antiplatelet or treatment with alteplase (AUST 2005; DEFUSE 2018; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MR CLEAN 2015; MR RESCUE 2013; PROACT 2 1999; REVASCAT 2015; SWIFT PRIME 2015).

There were also differences in the use of heparin. In PROACT 1 1998, participants in both the intervention and control groups received heparin. In 11 studies heparin was only given to participants in the intervention group who underwent angiography (AUST 2005; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 2 1999; REVASCAT 2015; SWIFT PRIME 2015).

Assessment of outcome

All studies reported death at the end of follow-up. Data were available for deaths in the acute phase from one study (MELT 2007). Functional outcome was assessed using the modified Rankin scale (mRS) in all included studies. All studies provided data on mRS score 0 to 2, with the exception of PROACT 1 1998, which only provided data on mRS score 0 to 1. All studies except AUST 2005 collected the outcomes of interest at 90 days.

The methods of determination of intracranial haemorrhage varied and are provided in the Characteristics of included studies table.

Nine studies reported recanalisation using the thrombolysis in cerebral infarction (TICI) or modified TICI classification (DAWN 2018; DEFUSE 2018; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; PISTE 2016; PROACT 1 1998; PROACT 2 1999; SWIFT PRIME 2015). TICI grade 3 is complete perfusion, and TICI grade 2 is partial perfusion. MELT 2007 reported recanalisation as:

1. complete;
2. partial and less than 50% in the affected territory;
3. partial and at least 50% in the affected territory; and
4. no recanalisation.

AUST 2005 did not prespecify criteria for judging recanalisation, although recanalisation at days 7 to 10 was a prespecified secondary outcome. Recanalisation was described as either complete or partial.

Results of the search

The search yielded 11,062 articles, of which four studies were included in the previous version of this review (O'Rourke 2010). A total of 57 articles were assessed as potentially eligible and retrieved in full text. We excluded 31 studies because they were not RCTs of endovascular stroke therapies. Upon closer examination of the remaining 26 studies, we excluded seven studies because they compared endovascular therapy with other therapies (such as intravenous thrombolytic treatment) and were not eligible for inclusion in the present meta-analysis (Ducrocq 2005; Keris 2001; Lewandowski 1999; Sen 2009; SYNTHESIS Expansion 2013; SYNTHESIS pilot 2010; Wolfe 2008).

We identified six ongoing studies (ISRCTN19922220; NCT01717755; NCT01852201; NCT02419781; NCT03094715; NCT03805308).

A PRISMA study flow diagram is shown in Figure 1.

Figure 1. PRISMA study flow diagram.

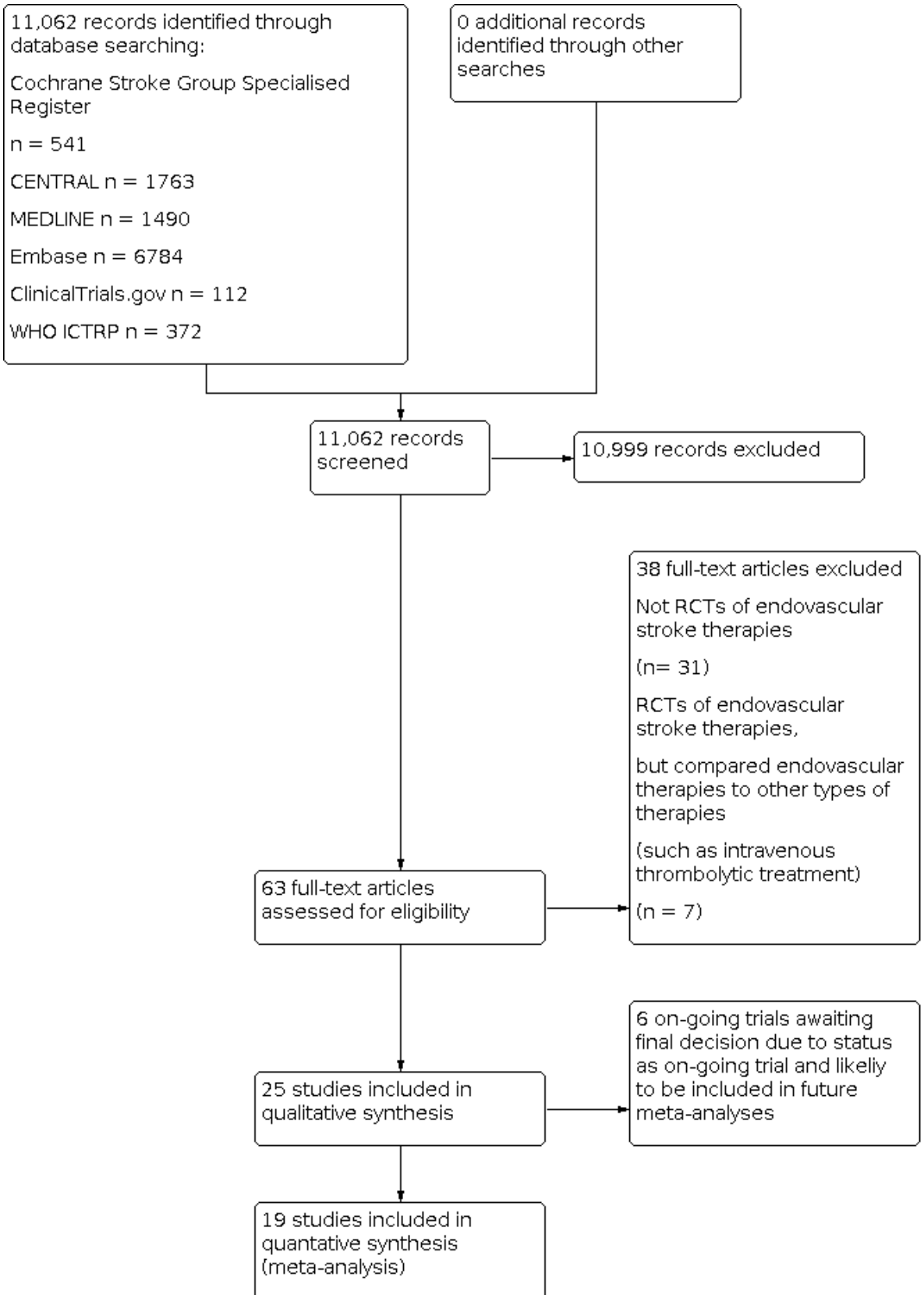
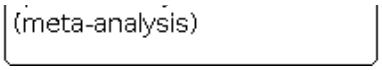


Figure 1. (Continued)



Included studies

We included 19 studies in the review (see Characteristics of included studies) (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016).

All trials except AUST 2005 collected the outcomes of interest at 90 days' follow-up.

Excluded studies

We excluded seven studies (see Characteristics of excluded studies) (Ducrocq 2005; Keris 2001; Lewandowski 1999; Sen 2009; SYNTHESIS Expansion 2013; SYNTHESIS pilot 2010; Wolfe 2008).

Risk of bias in included studies

The quality of randomisation was adequate in 15 studies (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THRACE 2016). The quality of randomisation was unclear in four studies, as the studies did not report the precise methodology of sequence generation (AUST 2005; MELT 2007; PROACT 1 1998; THERAPY 2016).

A total of 20 participants were lost to follow-up in the 19 included trials. One trial did not report ITT analyses (PROACT 1 1998), and one trial did not report on their prespecified secondary outcomes (AUST 2005).

Sixteen trials were terminated early either due to efficacy or lack of equipoise and consequently suffered from a lack of statistical power (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; PISTE 2016; PROACT 1 1998; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). For details, see Characteristics of included studies.

Allocation

The quality of randomisation was adequate in 15 studies (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THRACE 2016). The quality of randomisation was unclear in four studies, as the studies did not report the precise methodology of sequence generation (AUST 2005; MELT 2007; PROACT 1 1998; THERAPY 2016).

We assessed 16 studies as at low risk of bias (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THRACE 2016), and three studies as at unclear risk of bias (AUST 2005; EXTEND-IA 2015; THERAPY 2016).

Blinding

In only one trial (PROACT 1 1998) were the participants and personnel blinded for treatment. We assessed the other 18 studies to be of unclear risk of bias (perfomance bias) (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). Even though the nature of the intervention makes it difficult both practically and ethically to perform double-blind studies this is a source of bias. We assessed 17 studies to be at low risk of bias (detection bias) (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016), and two studies to be of high risk of bias (EASI 2017; THRACE 2016). In EASI 2017, all data and outcome measures were collected by unblinded routine care personnel, and in THRACE 2016, outcome assessment was performed by vascular neurologists not masked to the allocated treatment.

Incomplete outcome data

We assessed 13 studies as at low risk (AUST 2005; BEST 2019; DAWN 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015); four trials as at an unclear risk (DEFUSE 2018; PISTE 2016; THERAPY 2016; THRACE 2016); and two trials as at high risk of attrition bias (MR RESCUE 2013; PROACT 1 1998). MR RESCUE 2013 presented per-protocol analyses, and nine participants were excluded from the analyses (five did not have target lesion on vessel imaging; two did not have post-tPA vessel imaging; and two had failed perfusion imaging). PROACT 1 1998 did not report the primary efficacy outcome for six randomised but untreated participants (i.e. an on-treatment rather than the preferred ITT analysis). Of these six participants, five were in the treatment group, representing 16% of the total randomised treatment group; the remaining randomised but untreated participant was in the placebo group. Given the possibility that the five participants randomised to the treatment group who did not receive treatment represented a subgroup of non-responders, this may have had the effect of enriching the treatment group with responders and biasing the results in favour of treatment. The primary safety outcome was reported for these six participants, therefore we do not consider that the safety analysis was prone to on-treatment bias.

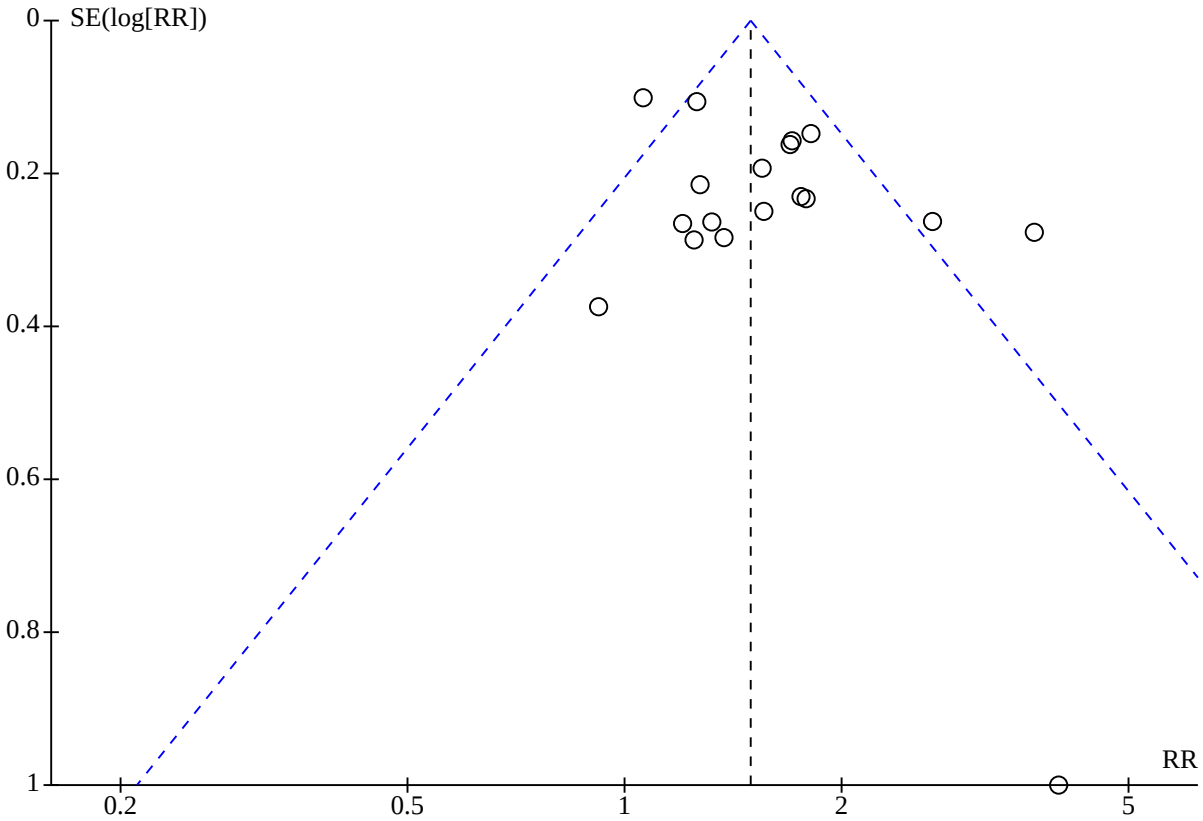
Selective reporting

Four studies were not analysed according to the ITT principle (ESCAPE 2015; PROACT 1 1998; SWIFT PRIME 2015; THERAPY 2016). We assessed 17 studies to be at low risk (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016), and one study to be at unclear risk of reporting bias (THRACE 2016). We assessed one study to be

at high risk of bias because this trial did not report prespecified secondary outcomes (AUST 2005). Baseline angiographic findings were not reported for two participants. There was no a priori requirement for follow-up imaging in this study.

We explored publication bias by inspecting the funnel plot (Figure 2). We considered the funnel plot visually symmetric.

Figure 2. Funnel plot of comparison: Favourable functional outcome at end of follow-up (functional outcome: mRS 0 to 2).



Other potential sources of bias

A total of 20 participants were lost to follow-up in the 19 included studies. Sixteen trials were terminated early either due to efficacy or lack of equipoise, and thus suffered from a lack of statistical power (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; PISTE 2016; PROACT 1 1998; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). We assessed eight studies to be at low risk (DAWN 2018; DEFUSE 2018; PISTE 2016; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016), and 11 studies to be at unclear risk of other bias (AUST 2005; BEST 2019; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PROACT 2 1999). We assessed one study to be at high risk of other bias (PROACT 1 1998). This study did not report the primary efficacy outcome for six randomised but untreated participants (i.e. an on-treatment rather than the preferred ITT analysis). Of these six participants, five were in the treatment group, representing 16% of the total randomised treatment group; the remaining randomised but untreated participant was in the placebo group. Given the possibility that the five participants randomised to the treatment group who did not receive treatment represented a subgroup of non-responders, this may have had the effect of enriching the treatment group with responders and biasing the results in favour of treatment. The primary safety outcome was reported for these six participants, therefore we do not consider that the safety analysis was prone to on-treatment bias. Any on-treatment bias due to these six participants would be diluted in the overall analysis. Also, this trial was stopped early by the sponsor to determine whether there was sufficient evidence of safety and efficacy to support continuation of a longer-term programme, which was ultimately expressed in the form of the phase III PROACT 2 1999 trial. No safety concerns were involved in that decision. An analysis of the data set from all participants who underwent angiography by a biostatistical unit independent of the conduct of the trial forms the basis of the published PROACT 1 1998 report. At the time of termination, the PROACT 1 1998 trial had achieved 89% of its target sample size. The implications are difficult to interpret. As a general principle, trials that are stopped for any reason other than according to specific predefined stopping rules are theoretically prone to bias. However, it remains unclear whether this factor introduced any bias in this particular case.

Effects of interventions

See: **Summary of findings 1** Endovascular thrombectomy interventions compared to standard therapy for acute ischaemic stroke

Favourable functional outcome at the end of follow-up

For mRS 0 to 2, data were available for a total of 3715 participants from 18 trials (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). There was overall an effect in favour of treatment (risk ratio (RR) 1.50, 95% confidence interval (CI) 1.37 to 1.63; 3715 participants, 18 RCTs; high-certainty evidence) with moderate between-study heterogeneity (I^2 = 56%) (Analysis 1.1).

For mRS 0 to 1, data were available for a total of 3632 participants from 18 trials (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). There was a high effect in favour of treatment (RR 1.61, 95% CI 1.42 to 1.82, 3632 participants, 18 RCTs) with moderate between-study heterogeneity (I^2 = 38%) (Analysis 1.2).

Death from all causes at the end of follow-up

Data were available for a total of 3793 participants from all 19 trials (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). There was a reduced risk of death in the treatment group (RR 0.85, 95% CI 0.75 to 0.97; 3793 participants, 19 RCTs; high-certainty evidence) with little between-study heterogeneity (I^2 = 0%) (Analysis 2.1).

Death from all causes during the acute phase

Data were available for a total of 1243 participants from three trials (IMS III 2013; MELT 2007; MR CLEAN 2015). There was no evidence of an effect of treatment on deaths in the acute phase (RR 1.06, 95% CI 0.77 to 1.47; 1243 participants, 3 RCTs) with I^2 = 0% (Analysis 2.2).

Symptomatic intracranial haemorrhage during the acute phase

Data were available for a total of 1559 participants from six trials (DAWN 2018; IMS III 2013; MR RESCUE 2013; PROACT 1 1998; PROACT 2 1999; THRACE 2016). We observed no excess risk of symptomatic intracranial haemorrhage in the treatment group (RR 1.46, 95% CI 0.91 to 2.36; 1559 participants, 6 RCTs) with very little between-study heterogeneity (I^2 = 0%) (Analysis 3.1).

Symptomatic intracranial haemorrhage at the end of follow-up

Data were available for a total of 1752 participants from 10 trials (DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; PISTE 2016; PROACT 1 1998; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016). We observed no excess risk of intracranial haemorrhage in the treatment group (RR 1.05, 95% CI 0.72 to 1.52; 1752 participants, 10 RCTs; high-certainty evidence) with no between-study heterogeneity (I^2 = 0%) (Analysis 3.2).

Neurological outcome at the end of follow-up

NIHSS data were available for a total of 334 participants from three trials (MELT 2007; PROACT 1 1998; PROACT 2 1999). There was an effect in favour of treatment (RR 2.03, 95% CI 1.21 to 3.40; 334 participants, 3 RCTs; moderate-certainty evidence) with no between-study heterogeneity (I^2 = 0%) (Analysis 4.1).

Degree of recanalisation

Data on complete recanalisation (TIMI grade 3) were available for 198 participants from two trials (PROACT 1 1998; PROACT 2 1999). For TIMI grade 3, there was an overall effect in favour of treatment (RR 8.25, 95% CI 1.63 to 41.90; 198 participants, 2 RCTs; moderate-certainty evidence) with no between-study heterogeneity (I^2 = 0%) (Analysis 5.1).

Data on complete or complete or partial recanalisation (TICI grade 2 or 3) were available for 974 participants randomised to treatment from 10 trials (DAWN 2018; DEFUSE 2018; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; PISTE 2016; PROACT 1 1998; PROACT 2 1999; SWIFT PRIME 2015; THERAPY 2016), and for 99 participants randomised to control from three trials (EXTEND-IA 2015; PROACT 1 1998; PROACT 2 1999). In the three trials that provided data on TIMI 2 or 3 for both the treatment group and the controls (total 268 participants) (EXTEND-IA 2015; PROACT 1 1998; PROACT 2 1999), there was an effect in favour of treatment (RR 3.11, 95% CI 2.18 to 4.42; P < 0.00001; 268 participants, 3 RCTs) with moderate between-study heterogeneity (I^2 = 48%) Analysis 5.2.

Major extracranial haemorrhage during the acute phase

In PROACT 1 1998, two participants had severe injection site haemorrhages; however, the allocation of these participants was unclear. No participants in MELT 2007 had major extracranial haemorrhage in the acute phase. In THRACE 2016, three participants had groin haematoma, and in RESILIENT 2020, one participant in the intervention group had groin haematoma. In DAWN 2018, one participant had access-site complications leading to intervention. In ESCAPE 2015, three participants in the intervention group had haematomas at the access site. In EXTEND-IA 2015, one participant had groin/retroperitoneal haematoma and was given a blood transfusion. In MR CLEAN 2015, two participants in the control group had major extracranial haemorrhage. In REVASCAT 2015, five participants in the control group had extracranial haemorrhage. It was unclear whether any participants in the following nine studies had major extracranial haemorrhages in the acute phase: AUST 2005; BEST 2019; DEFUSE 2018; EASI 2017; IMS III 2013; MR RESCUE 2013; PROACT 2 1999; SWIFT PRIME 2015; THERAPY 2016.

Subgroup analyses

Age and sex

There was no difference in the effects of the intervention between younger and older participants in the nine trials that provided subgroup data on age (RR 1.72, 95% CI 1.48 to 2.0 versus RR 1.49, 95% CI 1.18 to 1.87; P for interaction = 0.29) (DAWN 2018; DEFUSE 2018; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THRACE 2016). The cutoff for younger and older participants varied between the trials, from 66

years in IMS III 2013 to 80 years in ESCAPE 2015 and MR CLEAN 2015 (Analysis 6.1).

There were no differences in the effects of the intervention between women and men in the seven trials that provided subgroup data on sex (RR 1.67, 95% CI 1.37 to 2.04 versus RR 1.63, 95% CI 1.34 to 1.98; P for interaction = 0.85) (Analysis 6.2) (DAWN 2018; DEFUSE 2018; ESCAPE 2015; IMS III 2013; RESILIENT 2020; SWIFT PRIME 2015; THRACE 2016).

Stroke severity

Participants with higher NIHSS scores had a better effect of the intervention than participants with lower NIHSS scores in the nine trials that provided subgroup data on NIHSS score (RR 1.42, 95% CI 1.22 to 1.66 versus RR 2.0, 95% CI 1.57 to 2.55; P for interaction = 0.02) (DAWN 2018; DEFUSE 2018; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THRACE 2016). The cutoff for NIHSS score varied from 17 to 21 (Analysis 6.3).

Early ischaemic change

There was a better effect of the intervention in participants with more pronounced early ischaemic changes on CT (lower ASPECTS) than in those with less early ischaemic changes on CT (higher ASPECTS) in the six trials that provided subgroup data on ASPECTS (RR 2.01, 95% CI 1.53 to 2.66 versus RR 1.39, 95% CI 1.19 to 1.62; P for interaction = 0.02) (ESCAPE 2015; IMS III 2013; MR CLEAN 2015; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015). The cutoff for ASPECTS varied from 7 in ESCAPE 2015 and REVASCAT 2015 to 8 in IMS III 2013, MR CLEAN 2015, and SWIFT PRIME 2015 (Analysis 6.4).

Time to intervention

There was no difference between the effect of intervention in trials with a shorter mean or median time (< 250 minutes) to start of intervention (RR 1.67, 95% CI 1.40 to 2.00) (ESCAPE 2015; EXTEND-IA 2015; MELT 2007; SWIFT PRIME 2015); medium time (250 to 300 minutes) (RR 1.30, 95% CI 1.11 to 1.51) (IMS III 2013; MR CLEAN 2015; REVASCAT 2015); and longer time (> 300 minutes) to start of intervention (RR 1.41, 95% CI 0.97 to 2.04; P for interaction = 0.10) (Analysis 6.5) (AUST 2005; MR RESCUE 2013; PROACT 1 1998; PROACT 2 1999).

Intravenous thrombolytic treatment before randomisation

There was no difference in the effect of the intervention between participants who had been given intravenous thrombolytic treatment compared to those who had not been given intravenous thrombolytic treatment before randomisation in the four trials that provided subgroup data on thrombolytic treatment (RR 1.95, 95% CI 1.55 to 2.46 versus RR 2.18, 95% CI 1.37 to 3.47; P = 0.67) (Analysis 6.6) (ESCAPE 2015; IMS III 2013; RESILIENT 2020).

Method of recanalisation

There were differences between the effect of the intervention in trials where participants were treated with intra-arterial thrombolysis alone without any endovascular mechanical thrombectomy (RR 1.47, 95% CI 1.08 to 1.99) (AUST 2005; MELT 2007; PROACT 1 1998; PROACT 2 1999); trials where a majority of participants were treated with first-generation mechanical devices other than stent retrievers (e.g. Merci and Penumbra systems) (RR 1.05, 95% CI 0.87 to 1.27) (IMS III 2013; MR RESCUE 2013); and trials where a majority of participants were treated with stent retrievers (RR 1.80, 95% CI 1.59 to 2.04; P for interaction < 0.001) (Analysis 6.7) (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; PISTE 2016; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015).

Proximity of vascular occlusion

There was a larger effect of the intervention in trials that included primarily proximal occlusion strokes, ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; REVASCAT 2015; SWIFT PRIME 2015, than in trials that included both proximal and non-proximal occlusion strokes, AUST 2005; IMS III 2013; MELT 2007; MR RESCUE 2013; PROACT 1 1998; PROACT 2 1999 (RR 1.71, 95% CI 1.47 to 1.99 versus RR 1.16, 95% CI 0.99 to 1.37; P for interaction < 0.001) (Analysis 6.8).

Infarct localisation

Some studies provided data on subgroups of stroke, but we were unable to compare these subgroups because of different definitions of stroke locations in each study (Analysis 6.9). Only one trial included participants with basilar artery occlusions (AUST 2005), but the sample size for this trial was too small for subgroup analyses.

Patient selection based on penumbra imaging

There was no difference in the effect of intervention between trials that used penumbra imaging for selection of patients to treatment (RR 2.24, 95% CI 1.45 to 3.46) DAWN 2018; DEFUSE 2018; EXTEND-IA 2015; MR RESCUE 2013; SWIFT PRIME 2015, and trials that did not use penumbra imaging (RR 1.72, 95% CI 1.42 to 2.08; P for interaction = 0.27) (Analysis 6.10) (AUST 2005; ESCAPE 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; PROACT 1 1998; PROACT 2 1999; REVASCAT 2015).

Sensitivity analyses

There was no difference in participants with good functional outcome between trials included the previous version of the review (AUST 2005; MELT 2007; PROACT 1 1998; PROACT 2 1999), compared with trials included in the current review (RR 1.47, 95% CI 1.08 to 1.99 versus RR 1.50, 95% CI 1.37 to 1.63; P for interaction = 0.91) (Analysis 7.1) (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016).

There was no difference in participants with good functional outcome between trials that included all planned participants (MR CLEAN 2015; MR RESCUE 2013; PROACT 2 1999), compared with trials that were stopped early (RR 1.55, 95% CI 1.22 to 1.98 versus RR 1.54, 95% CI 1.39 to 1.70; P for interaction = 0.95) (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; PISTE 2016; PROACT 1 1998; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016).

The sensitivity analysis using a random-effects model (Analysis 7.3) found similar results compared to the fixed-effect model (Analysis 1.1). The RR was 1.54 (95% CI 1.33 to 1.78) in the random-effects model compared to RR 1.50 (95% CI 1.37 to 1.63) in the fixed-effect model.

DISCUSSION

Summary of main results

Since the first version of this review, we have added 15 new studies, bringing the total number of studies to 19, and the total number of participants up from 350 to 3793. With this substantial increase in evidence from randomised controlled trials, it has become clear that endovascular thrombectomy conveys important clinical benefits, with an increase in the chance of a good functional outcome (modified Rankin Scale score 0 to 2), and with no increase in the risk of symptomatic intracranial haemorrhage or death; there was in fact a reduction in the risk of death. The trials were generally of high methodological quality with low to unclear risk of bias, and the results were consistent with very little statistical heterogeneity, meaning that clinicians can be confident that the same results will apply in clinical practice, if similar patients are given similar treatment, in similar acute stroke services.

Subgroup analyses showed that the results apply irrespective of whether or not the participants had received intravenous thrombolytic therapy before the intervention, and irrespective of age and sex. Data were insufficient to determine the latest time for treatment to be effective, but subgroup analysis indicated that the results were better in participants with clinically more severe stroke, and in those with more pronounced early ischaemic changes on CT. Our subgroup analysis of four trials with 350 participants showed effect and benefit for functional outcome for intra-arterial thrombolysis, which adds important information to the ongoing discussion regarding treatment with intra-arterial thrombolysis for acute ischaemic stroke.

Overall completeness and applicability of evidence

The majority of participants in the included trials had anterior circulation infarcts caused by thrombotic occlusions in a proximal cerebral artery, as verified by CT or MRI angiography, and were treated within eight hours of symptom onset with the stent retriever technique. It is therefore uncertain whether the results can be extrapolated to individuals with posterior circulation infarcts, or to the use of other interventional techniques. Indeed, subgroup analysis showed a significantly lower effect amongst participants treated with techniques other than stent retrievers. We were not able to characterise the acute stroke services in which the participants were treated, so we cannot assess whether the results are limited to a certain organisation of services, or whether they apply irrespective of organisation.

Quality of the evidence

We prepared summary of findings tables using GRADE Pro GDT 2020 and Cochrane methods.

We are confident that the true effect lies close to that of the estimate of the effect.

The strengths of this review are that all of the included studies were either at a low or unclear risk of bias. A common source of heterogeneity in systematic reviews is differences in time of follow-up. All studies in our meta-analysis, with the exception of AUST 2005, measured outcome at 90 days' follow-up. This is therefore a strength of this review. As AUST 2005 included only 16 participants, we did not explore this in a subgroup analysis. Further, for all endovascular procedures there is a risk that no occlusions are identified for thrombectomy (Nogueira 2013). This may attenuate the results and may introduce bias.

The weaknesses of this review are that some studies were small, and studies included different types of endovascular treatments, such as either endovascular thrombectomy or intra-arterial interventions, or a combination of the two. Furthermore, only one trial was double-blinded (PROACT 1 1998). This trial was of intra-arterial thrombolysis and did not include mechanical thrombectomy. It is not possible to blind the interventionist when performing mechanical endovascular thrombectomy. Another weakness is that 16 trials were terminated prematurely and therefore lacked statistical power.

Potential biases in the review process

We minimised potential biases in the review process by searching for published and unpublished studies from several sources with no restriction on date of publication or language. Two review authors independently extracted data and conducted risk of bias assessment.

Agreements and disagreements with other studies or reviews

Our review is in line with two recently published systematic reviews of endovascular thrombectomy for acute ischaemic stroke, which showed positive effect of endovascular thrombectomy for acute ischaemic stroke (Lin 2019; Zhao 2020). With its thorough search strategies and identification of more studies than these two meta-analyses, our review adds to the literature.

AUTHORS' CONCLUSIONS

Implications for practice

We found high-certainty evidence that endovascular thrombectomy improves functional and neurological outcomes without increasing haemorrhage or death. The benefit was seen with/without intravenous thrombolysis and was unrelated to age, sex, and time to intervention (although most participants were treated within six hours of symptom onset). Benefits were greater with more severe stroke.

Implications for research

Very few trials included individuals with posterior circulation infarcts, but trials are underway that will try to answer whether similar benefits can be achieved in such patients (NCT01717755). New trials are also needed to confirm the maximum time window for endovascular thrombectomy to be effective, and how advanced imaging techniques should be used to identify patients who might benefit from treatment in the late hours after stroke onset. We also expect that with time and research development of endovascular thrombectomy, new techniques will emerge.

On a population level, there is a need to investigate whether a strategy of primary endovascular thrombectomy is superior to a strategy with primary intravenous thrombolytic treatment in a local centre followed by transfer of eligible patients to an interventional centre. If such a strategy is superior, what is the maximum time delay for primary endovascular thrombectomy intervention to be superior to intravenous thrombolysis followed by intervention?

Furthermore, endovascular thrombectomy is performed by professionals from many disciplines, including neuroradiologists, general interventional radiologists, neurologists, neurosurgeons, and cardiologists. It is unknown whether the effect of treatment depends on the professional background of the interventionalist or the annual number of procedures. This information is important for determining whether endovascular thrombectomy could be provided by interventional cardiologists or radiologists in smaller hospitals.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

AUST 2005

Study characteristics	
Methods	RCT
Participants	Patients with acute posterior circulation stroke, confirmed by digital subtraction angiography Glasgow Coma Scale score ≥ 9 Age 18 to 85 years
Interventions	Endovascular intra-arterial intervention (IA thrombolysis with UK) plus anticoagulation versus anticoagulation alone, within 24 hours of stroke onset. UK was given in increments of 100,000 IU to a maximum of 1,000,000 IU. All participants received intra-arterial heparin as a 5000-international unit bolus followed by infusion to maintain an APTT of 60 to 80 seconds for a minimum of 2 days, and then oral warfarin to maintain an INR of 1.5 to 2.5 for 6 months.
Outcomes	Primary outcome: death or disability (Barthel Index and modified Rankin Scale scores) at 6 months Secondary outcomes: • degree of recanalisation at 7 to 10 days; • neurological impairment at 6 months; • safety and tolerability of intra-arterial UK; • cost-effectiveness of therapy.
Funding source	Unrestricted educational grant from Serono and by an intramural grant from the National Health and Medical Research Council of Australia

AUST 2005 *(Continued)*

Notes	There was no clear definition of sICH.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation by telephone with a central office, and subsequently by the pharmacy department at the Royal Melbourne Hospital. In 2 cases participants were randomised by coin toss in the treating centre, a practice approved by the trial steering committee. Concealment of allocation was considered to be adequate in each case, but a lack of detail with regard to the randomisation methodology used by the trial sponsor and Royal Melbourne Hospital pharmacy department means that it remains unclear whether sequence generation was satisfactory.
Allocation concealment (selection bias)	Unclear risk	Randomisation by telephone with a central office, and subsequently by the pharmacy department at the Royal Melbourne Hospital. In 2 cases participants were randomised by coin toss in the treating centre, a practice approved by the trial steering committee. Concealment of allocated treatment was considered to be adequate in each case, but a lack of detail with regard to the randomisation methodology used by the trial sponsor and Royal Melbourne Hospital pharmacy department means that it remains unclear whether sequence generation was satisfactory.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). All outcomes were determined by an independent outcomes committee who were blinded to treatment allocation. Clinical outcomes were determined at 6 months by a certified research nurse or a neurologist blinded to treatment allocation and who was not involved in the participant's initial care.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to clinical follow-up
Selective reporting (reporting bias)	High risk	Secondary outcomes not reported. Baseline angiographic findings not reported for 2 participants. No a priori requirement for follow-up imaging
Other bias	Unclear risk	The trial was stopped early because of slow recruitment and the withdrawal from sale of urokinase.

BEST 2019

Study characteristics

Methods	Randomised controlled, multicentre, open-label trial at 28 centres in China
Participants	Patients presenting within 8 hours of vertebrobasilar occlusion
Interventions	Endovascular therapy plus standard medical treatment or standard medical therapy alone. The endovascular procedure consisted of mechanical thrombectomy with stent retriever (the preferred method) or thrombo-aspiration devices.
Outcomes	Primary outcome: modified Rankin Scale score of 3 or lower at 90 days assessed on an intention-to-treat basis

BEST 2019 *(Continued)*

Funding source	Jiangsu Provincial Special Program of Medical Science
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation and stratified by participating centres
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias)Assessment was done by certified rater not aware of the trial group assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up. Reported all participants and intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Unclear risk	The trial was terminated prematurely by the steering committee based on recommendations from the data and safety monitoring board regarding excessive cross-overs and progressive drop in the average rate of valid per-centre recruitment.

DAWN 2018

Study characteristics

Methods	Randomised, multicentre, open-label, controlled phase II/III, treatment trial
Participants	Clinical signs and symptoms consistent with the diagnosis of an acute ischaemic stroke, and participant belongs to one of the following subgroups: (1) participant has failed IV-tPA therapy (defined as a confirmed persistent occlusion 60 minutes after administration), (2) participant is contraindicated for IV-tPA administration Age ≥ 18 years Baseline NIHSS ≥ 10 (assessed within 1 hour prior to measuring core infarct volume) Participant may be randomised between 6 to 24 hours after time last known well. No significant pre-stroke disability (pre-stroke mRS must be 0 or 1) Infarction < 1/3 MCA territory involved, as evidenced by CT or MRI
Interventions	Endovascular thrombectomy treatment (Trevo stent) plus best medical management vs best medical management. Thrombectomy was performed with the use of the Trevo device, a retrievable stent. Rescue reperfusion therapy or pharmacological agents were not permitted.
Outcomes	Weighted modified Rankin Scale score at 90 days follow-up
Funding source	Stryker Neurovascular
Notes	Terminated early due to efficacy

DAWN 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed with a central web-based procedure with block minimisation to balance the 2 groups and stratified according to mismatch criteria.
Allocation concealment (selection bias)	Low risk	Quote from protocol: "If the subject's eligibility status is confirmed, the server allocates the treatment"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias)Outcome assessment was performed by certified assessors unaware of treatment assignment. Adjudication performed by an independent clinical-events committee.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up. Reported all participants and intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Low risk	At 31 months and 206 participants enrolled, the trial was stopped prematurely because of the results of a prespecified interim analysis.

DEFUSE 2018

Study characteristics	
Methods	Multicentre, randomised, open-label trial with blinded outcome assessment
Participants	Patients with acute ischaemic stroke presenting between 6 and 16 hours from last known well and with remaining brain tissue that was not yet infarcted. Patients with proximal MCA or internal carotid artery occlusion, an initial infarct size of less than 70 mL, and a ratio of the volume of the ischaemic tissue on perfusion imaging to infarct volume of 1.8 or more
Interventions	Endovascular therapy (thrombectomy) plus standard medical treatment vs standard medical treatment alone. Thrombectomy was performed with any Food and Drug Administration-approved thrombectomy device at the discretion of the neurointerventionalist. Intra-arterial tissue plasminogen activator was not allowed.
Outcomes	Primary outcome: ordinal core on the modified Rankin Scale at 90 days follow-up
Funding source	National Institute of Neurological Disorders and Stroke
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based, dynamic randomisation system. Stratified according to age, core infarct volume, time from symptom onset to enrolment, baseline NIHSS, and trial site

DEFUSE 2018 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote from protocol: "When a new patient is enrolled, the site enters the stratification factor values into the electronic case report form (eCRF) on WebDCU. The dynamic randomization algorithm determines an imbalance measure for each treatment group". Allocation is done by the server after enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Outcome assessed by certified rater who was blinded to trial assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants lost to follow-up and intention-to-treat analysis provided.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Low risk	After an early interim analysis following the DAWN trial results and at 182 randomised participants, the trial was halted due to efficacy.

EASI 2017

Study characteristics	
Methods	Randomised, open-label, controlled phase III, treatment trial
Participants	Age ≥ 18 years NIHSS ≥ 8 Onset of symptoms is less than 5 hours or symptom/imaging mismatch Suspected occlusion of the M1 or M2 segment of the MCA, supraclinoid internal carotid artery, or basilar trunk
Interventions	Standard care plus mechanical thrombectomy versus standard care alone. Thrombectomy was performed under local or general anaesthesia using any approved device according to local practice.
Outcomes	Favourable functional outcome, defined as modified Rankin Scale score 0 to 2 at 90 days follow-up
Funding source	No funding source for this study
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-based. Minimisation procedure was used as a method of adaptive stratified sampling.
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). All data and outcome measures were collected by unblinded routine care personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up and intention-to-treat analysis provided.

EASI 2017 *(Continued)*

Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Unclear risk	Randomised allocation stopped November 2014 when benefit was shown by other trials. 10 participants randomised to interventional management did not receive this. 3 participants were cross-overs from standard treatment to intervention.

ESCAPE 2015

Study characteristics	
Methods	RCT
Participants	Patients with a proximal intracranial occlusion in the anterior circulation were included up to 12 hours after symptom onset. Patients with a large infarct core or poor collateral circulation on CT and CT angiography were excluded.
Interventions	Standard care according to local guidelines (control group) Standard care plus endovascular thrombectomy intervention with the use of available thrombectomy devices (intervention group). The neurointerventionalist used available thrombectomy devices to achieve reperfusion. The use of retrievable stents was recommended. Suction through a balloon guide catheter in the relevant internal carotid artery during thrombus retrieval was recommended.
Outcomes	Primary outcome was modified Rankin Scale score at 90 days. Secondary outcomes were NIHSS score 0 to 2 at 90 days follow-up, Barthel Index score 95 to 100 at 90 days follow-up, TICI score 2b/3 at final angiogram in the intervention group. EuroQoL 5-Dimension (EQ-5D) self-report questionnaire at 90 days follow-up. Serious adverse events were death at 90 days follow-up, large or malignant MCA stroke, sICH, haemorrhage at access site, and perforation of the MCA.
Funding source	Funded by Cividien and others
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Real-time, dynamic, internet-based, randomisation with minimisation procedure to achieve distribution balance with regard to age, sex, baseline NIHSS score (range 0 to 42), site of arterial occlusion, baseline ASPECT score, and status with respect to intravenous alteplase treatment
Allocation concealment (selection bias)	Low risk	Quote from protocol: "Because randomisation will occure dynamically in real-time, it will be fully concealed"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Clinical outcomes were assessed by trained personnel blinded to treatment allocation. Interpretation of images was performed at an external core laboratory by personnel blinded to treatment allocation.

ESCAPE 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants (1.3%) were lost to follow-up. Missing outcome data for these participants were not imputed.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses
Other bias	Unclear risk	The trial was stopped early because of evidence of efficacy after an interim analysis following the MR CLEAN results and at 316 randomised participants.

EXTEND-IA 2015

Study characteristics	
Methods	RCT
Participants	Patients were eligible if they could receive intravenous alteplase within 4.5 hours after the onset of anterior circulation ischaemic stroke and had occlusion of the internal carotid artery or of the first or second segment of the MCA, as seen on CT angiography. Patients were eligible if CT perfusion imaging showed salvageable brain tissue and ischaemic core of < 70 mL. Intervention had to be initiated (groin puncture) within 6 hours after stroke onset and completed within 8 hours after onset. There were no restrictions on age or clinical severity according to NIHSS score. Participants were required to have functional independence before the stroke episode, defined as mRS score 0 to 2.
Interventions	Thrombectomy with the Solitaire FR (Flow Restoration) stent retriever (intervention group) No intra-arterial treatment (controls) All participants received 0.9 mg of alteplase per kilogram of body weight less than 4.5 hours after the onset of ischaemic stroke.
Outcomes	Primary outcomes: • reperfusion at 24 hours; and • early neurological improvement (defined as reduction of NIHSS score ≥ 8 or score 0 to 1 at day 3). Secondary outcomes: death, mRS score at 90 days follow-up, and sICH
Funding source	Australian National Health and Medical Research Council and others
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation procedure was computer-generated randomisation code lists, with stratification for site of baseline arterial occlusion.
Allocation concealment (selection bias)	Low risk	Quote from protocol: "once patient recruitment data are submitted by the site staff via EXTEND-IA online, the randomization iss immediately provided back to the investigator."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Radiological outcome measures were centrally analysed, blinded to assigned treatment. Neurological impair-

EXTEND-IA 2015 *(Continued)*

		ment and functional scores were measured by a clinician blinded to assigned intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up and intention-to-treat analysis provided.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Unclear risk	The trial was stopped early because of evidence of efficacy after 70 participants had undergone randomisation and because of the publication of MR CLEAN.

IMS III 2013

Study characteristics	
Methods	RCT
Participants	Patients who had received intravenous r-tPA within 3 hours after symptom onset. In the first part of the study, patients were eligible if they had an NIHSS score of 10 or higher. After 284 of the 656 participants were included, identification of occlusion with the use of CT angiography was allowed to determine trial eligibility for patients with an NIHSS score of 8 or 9.
Interventions	All participants received intravenous r-tPA (0.9 mg/kg), with 10% as a bolus and the remainder infused over a 1-hour period (maximum dose 90 mg). Randomisation was required within 40 minutes after the initiation of the infusion. Participants randomly assigned to IV r-tPA received the remainder of the standard dose. In the first part of the trial, participants randomised to the endovascular thrombectomy intervention only received 2/3 of the standard IV dose, plus any r-tPA given intra-arterially. During the latter part of the trial, participants randomised to the endovascular intervention received the full standard IV dose. The angiographic procedure had to begin within 5 hours and be completed within 7 hours after the onset of stroke. Heparin infusion was started intravenously with a 2000-unit bolus, followed by an infusion of 450 units per hour during endovascular therapy, and was discontinued at the end of the procedure. The method of endovascular intervention was determined by the neurointerventionalist, who could choose between mechanical thrombectomy with stent retrievers, Penumbra system or Solitaire FR revascularisation device or endovascular intra-arterial delivery of tPA by means of microcatheter.
Outcomes	modified Rankin Scale score of 2 or less at 90 days
Funding source	National Institutes of Health and others
Notes	The planned sample size was 900 participants.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-based randomisation using a computer-based algorithm.
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelope".

IMS III 2013 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Outcome assessment was by personnel blinded to allocated treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	An unfavourable imputation was applied for 27 participants (14 participants for whom the primary outcome was assessed outside the specified 30-day window, and 13 for whom the primary outcome was not assessed).Intention-to-treat analysis was provided.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Unclear risk	The study was stopped early because of futility after 656 participants had undergone randomisation following a prespecified rule. A total of 23% participants randomised to intervention did not receive thrombectomy because there was no lesion identified during the endovascular procedure.

MELT 2007

Study characteristics	
Methods	RCT
Participants	Acute MCA territory ischaemic stroke allowing initiation of treatment within 6 hours of stroke onset Participants were randomised when digital subtraction angiography of the symptomatic carotid artery territory showed complete occlusion of either the horizontal M1 or the M2 division of the MCA. NIHSS at least 5 Age 20 to 75 years
Interventions	Intra-arterial thrombolysis with urokinase ± mechanical clot disruption with guidewire vs no such treatment, against a background of standard medical care not including IV-tPA. 5000 IU heparin were infused prior to introducing the angiogram sheath. The microcatheter was passed through the clot, and urokinase was infused beyond the distal margin of the thrombus as repeated boluses of 120,000 IU over 5 minutes to a maximum of 600,000 IU, which were discontinued if complete recanalisation was achieved. Antithrombotic therapies including heparin, warfarin, and aspirin were prohibited for 24 hours after thrombolysis in the treatment group.
Outcomes	Primary outcome: favourable clinical outcome, defined as mRS score of 0 to 2 at 3 months Secondary outcomes: • sICH within 24 hours of starting treatment; • degree of recanalisation; • NIHSS score 0 to 1 at 24 hours, 30 days, 90 days; • Barthel Index score at least 95 at 30 days, 90 days; • mRS score 0 to 1 at 30 days, 90 days; • any haemorrhagic finding on CT.
Funding source	Grants-in-Aid from the Ministry of Health, Labor and Welfare of Japan
Notes	In this study sICH was defined as CT evidence of apparent neurological deterioration manifesting as either "objective signs" or an increase of at least 4 points from the most recent NIHSS score. As has been previously pointed out (Saver 2007), the process for adjudicating new "objective signs" is not well delineated and confounds direct comparison with National Institute of Neurologic Diseases and Stroke-defined sICH rates.

MELT 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation by a central randomisation centre via the internet, but the precise methodology used for randomisation was not explained, therefore it remains unclear whether sequence generation was adequate.
Allocation concealment (selection bias)	Low risk	Central randomisation via internet
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). All angiograms were evaluated by the film reading committee, who were unaware of the clinical information. Clinical outcome was assessed by physicians unaware of the treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat results presented. 1 participant was not randomised due to computer error. No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Unclear risk	The trial was stopped early by the steering committee following a recommendation by the independent monitoring committee when IV-tPA became available in Japan. The recommendation was that the trial be either modified so as not to include patients presenting within 3 hours of stroke onset, or terminated. We did not consider this to be a potential source of bias. No information provided regarding conventional vascular risk factors possibly related to outcome.

MR CLEAN 2015

Study characteristics

Methods	RCT
Participants	A clinical diagnosis of acute stroke, with a deficit on the NIHSS of 2 points or more CT or MRI scan ruling out intracranial haemorrhage Intracranial arterial occlusion of the distal intracranial carotid artery or middle (M1/M2) or anterior (A1/A2) cerebral artery, demonstrated with CT angiography, magnetic resonance angiography, digital subtraction angiography, or transcranial Doppler/duplex The possibility to start treatment within 6 hours from onset Informed consent given Age 18 years or over
Interventions	Approved intervention was both intra-arterial treatment, which consisted of arterial catheterisation with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, or mechanical thrombectomy, or both. The method of endovascular intervention was left to the discretion of the local neurointerventionist. The use of alteplase and UK for intra-arterial thrombolysis was allowed in this trial with a maximum dose of 90 mg of alteplase and 1,200,000 IU of UK. Mechanical treatment could involve thrombus retraction, aspiration, wire disruption, or use of a retrievable stent. Endovascular intervention plus best medical therapy vs best medical therapy alone

MR CLEAN 2015 *(Continued)*

Outcomes	Score on the modified Rankin Scale at 3 months
Funding source	Dutch Heart Foundation and others
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer- and web-based randomisation with the use of permuted blocks. Stratified according to medical centre, use of intravenous alteplase, planned treatment method, and stroke severity
Allocation concealment (selection bias)	Low risk	Randomisation done centrally over Internet or telephone after patient has been included.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Blinded outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants lost to follow-up (withdrew consent after randomisation), and intention-to-treat analysis provided
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses
Other bias	Low risk	Not terminated prematurely

MR RESCUE 2013

Study characteristics

Methods	RCT
Participants	New focal disabling neurologic deficit consistent with acute cerebral ischaemia (NIHSS ≥ 6) Age ≥ 18 ≤ 85 years Clot retrieval procedure can be initiated within 8 hours from onset Large vessel proximal anterior circulation occlusion on magnetic resonance imaging or CT angiography (internal carotid, M1 or M2 MCA) Pretreatment MRI performed according to MR RESCUE protocol Signed informed consent obtained from the patient or patient's legally authorised representative Premorbid modified Rankin Scale score of 0 to 2 Allowed but not required: patients treated with IV-tPA up to 4.5 hours from symptom onset with persistent target occlusion on post-treatment MR RESCUE MR or CT protocol performed at the completion of drug infusion (Note: rapidly improving neurological signs prior to randomisation is an exclusion)
Interventions	Mechanical thrombectomy (Merci Retriever or Penumbra System) plus best medical treatment vs best medical treatment. Participants in the embolectomy group could be treated with any combination of FDA-cleared embolectomy devices, including the Merci Retriever and the Penumbra System. Intra-arterial administration of tPA at a dose of as much as 14 mg was allowed as rescue therapy within 6 hours after symptom onset.
Outcomes	modified Rankin Scale score 0 to 2 at 90 days follow-up

MR RESCUE 2013 *(Continued)*

Funding source	National Institute of Neurological Disorders and Stroke
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation. Stratified according to penumbral pattern on brain imaging
Allocation concealment (selection bias)	Low risk	Central allocation through telephone after enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol analyses. 9 participants excluded from the analyses (5 did not have target lesion on vessel imaging; 2 did not have post-tPA vessel imaging; 2 had failed perfusion imaging).
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses
Other bias	Low risk	Not terminated prematurely

PISTE 2016

Study characteristics

Methods	Randomised controlled, multicentre, open-label, phase III treatment trial
Participants	Patients aged 18 years and older Clinically significant neurological deficit and NIHSS score ≥ 6 Enrolment, randomisation, and procedure commencement (groin puncture) possible within 90 minutes of the start of IV r-tPA treatment (groin puncture maximum 5.5 hours after stroke onset) Occlusion of the main MCA trunk, MCA bifurcation or intracranial internal carotid artery (carotid T, M1 or single proximal M2 branch) demonstrated on Computed Tomography Angiogram, Magnetic Resonance Angiogram or Digital Subtraction Angiography
Interventions	Mechanical thrombectomy vs best medical management. Both groups were given intravenous thrombolytic treatment.
Outcomes	modified Rankin Scale score 0 to 2 at 90 days follow-up
Funding source	Stroke Association, National Institute of Health Research Health Technology Assessment Programme, unrestricted grants from Codman and Covidien and others
Notes	Trial stopped early because of results from other trials.

Risk of bias

Bias	Authors' judgement	Support for judgement

PISTE 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-based randomisation with a minimisation algorithm for age, stroke severity, and symptom-onset to treatment time
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up. Intention-to-treat analysis provided.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses
Other bias	Low risk	Trial terminated early after review of other trial data.

PROACT 1 1998

Study characteristics	
Methods	RCT (phase II)
Participants	Acute MCA territory ischaemic stroke allowing initiation of treatment within 6 hours of stroke onset. Cerebral angiography of the symptomatic carotid artery territory had to show complete occlusion (TIMI grade 0) or contrast penetration with minimal perfusion (TIMI grade 1) of either the horizontal M1 or the M2 division of the middle cerebral artery. NIHSS 4 to 30, but patients with isolated aphasia or hemianopia were also included Age 18 to 85 years
Interventions	Intra-arterial thrombolysis with pro-UK versus no such treatment against a background of standard medical care not including IV-tPA. All participants received IV heparin for 4 hours after angiographic demonstration of an occluding thrombus. The rate of infusion varied throughout the trial as follows: the first 16 patients received a 100 IU/kg bolus followed by 1000 IU/hour infusion. On the recommendation of the external safety committee, the regimen was altered to a 2000-international unit bolus followed by 500 IU/hour infusion. Oral anticoagulants were prohibited for 24 hours following treatment. The PROACT method was to position the microcatheter in the proximal third of the target clot and thereby to infuse rpro-UK directly into the thrombus over a period of 120 minutes; the entire dose was given irrespective of any recanalisation achieved within the 120-minute infusion period. The dose of rpro-UK was 6 mg.
Outcomes	Primary efficacy outcome: recanalisation of M1 or M2 MCA at 120 minutes after initiation of treatment Primary safety outcome: sICH within 24 hours of treatment. Clinical outcome was assessed at 7, 30, and 90 days post-treatment (on-treatment analysis).
Funding source	Abbott Laboratories (Abbott Park, Ill) is the sponsor of the trial
Notes	The protocol for follow-up imaging in this study and PROACT 2 1999 is unclear.
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

PROACT 1 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Central randomisation centre assigned participants to the treatment or control groups, which we considered to be adequate concealment of allocation. However, the precise randomisation methodology was not explained, therefore it remains unclear whether sequence generation was adequate.
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind trial: control participants received IA saline placebo. All investigators and examining physicians were blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	No participants lost to follow-up. This study did not report the primary efficacy outcome for 6 randomised but untreated participants (i.e. an on-treatment rather than the preferred intention-to-treat analysis). 5 of these 6 participants were in the treatment group, representing 16% of the total randomised treatment group; the remaining randomised but untreated participant was in the placebo group. Given the possibility that the 5 participants randomised to the treatment group who did not receive treatment represent a subgroup of non-responders, this may have had the effect of enriching the treatment group with responders and biasing the results in favour of treatment. The primary safety outcome was reported for these 6 participants, therefore we do not consider that the safety analysis was prone to on-treatment bias. Any on-treatment bias due to these 6 participants would be diluted in the overall analysis.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.
Other bias	Unclear risk	No information provided regarding conventional vascular risk factors possibly related to outcome Trial stopped early by sponsor to determine whether there was sufficient evidence of safety and efficacy to support continuation of a longer-term programme, ultimately expressed in the form of the phase III PROACT 2 1999 trial. No safety concerns were involved in that decision. An analysis of the data set from all patients who underwent angiography by a biostatistical unit independent of the conduct of the trial forms the basis of the published PROACT 1 1998 report. At the time of termination, the PROACT 1 1998 trial had achieved 89% of its target sample size. The implications are difficult to interpret. As a general principle, trials that are stopped for any reason other than according to specific predefined stopping rules are theoretically prone to bias. However, it remains unclear whether this factor introduced any bias in this particular case.

PROACT 2 1999

Study characteristics	
Methods	RCT (phase III)
Participants	Acute MCA territory ischaemic stroke allowing initiation of treatment within 6 hours of stroke onset. TIMI grade 0 or 1 in either M1 or M2. NIHSS 4 to 30, or isolated aphasia or hemianopia Age 18 to 85 years
Interventions	Intra-arterial intervention with pro-urokinase versus no such treatment against a background of standard medical care not including IV-tPA. See PROACT 1 1998 for more details.
Outcomes	Primary outcome: favourable clinical outcome, defined as an mRS score of 0 to 2 at 3 months

PROACT 2 1999 *(Continued)*

	Secondary outcomes: • NIHSS 0 to 1 at 90 days; • rate of angiographic recanalisation; • at least 50% reduction in baseline NIHSS at 90 days; • Barthel Index scores of at least 60 at 90 days. Clinical outcomes were assessed in a standardised fashion at 7, 10, 30, and 90 days following randomisation by the same board-certified or "eligible" neurologist in each centre. All examiners were required to pass certifying examinations for the NIHSS and Barthel Index, with a requirement for NIHSS re-certification after approximately 6 months.
Funding source	Abbott Laboratories
Notes	Published analyses performed independently of the sponsor.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated master randomisation schedule using a random block size was used for sequence generation.
Allocation concealment (selection bias)	Low risk	A blinded randomisation code was assigned by telephone independent of the sponsor. The schedule was not stratified by clinical centre to preclude knowledge of the distribution of future treatment assignments at a given centre.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). All CT and 2-hour angiograms were assessed by a neuroradiologist at a core facility who was blinded to treatment assignment and clinical status. Follow-up examinations were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat results reported. Some participants carried forward. Some appropriate imputation used. No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.
Other bias	High risk	Significant excess of diabetics in control group. This is a potential source of bias.

RESILIENT 2020

Study characteristics

Methods	Randomised controlled, multicentre, open-label, prospective, blinded outcome evaluation trial
Participants	Patients with proximal arterial occlusion in the anterior circulation that could be treated within 8 hours after onset of stroke symptoms
Interventions	Standard care plus mechanical thrombectomy or standard care alone. In the intervention group, thrombectomy was performed with the Solitaire FR stent retriever or Penumbra aspiration system. Standard medical care including the use of intravenous alteplase followed national and AHA medical guidelines.

RESILIENT 2020 *(Continued)*

Outcomes	Primary outcome: disability at 90 days evaluated by the distribution of scores on the modified Rankin Scale
Funding source	Unrestricted grant from the Brazilian Ministry of Health
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed in real time by dynamic, internet-based procedure and with a minimisation algorithm.
Allocation concealment (selection bias)	Low risk	Central randomisation after patient had been recruited into the trial.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses were conducted according to the intention-to-treat principle. 1 participant lost to follow-up
Selective reporting (reporting bias)	Low risk	Reported prespecified outcomes
Other bias	Low risk	Trial was terminated early because of efficacy.

REVASCAT 2015

Study characteristics

Methods	RCT
Participants	Acute ischaemic stroke where patient is ineligible for IV thrombolytic treatment or the treatment is contraindicated (e.g. patient presents beyond recommended time from symptom onset), or where patient has received IV thrombolytic therapy without recanalisation after a minimum of 30 minutes from start of IV-tPA infusion No significant pre-stroke functional disability (mRS ≤ 1) Baseline NIHSS score obtained prior to randomisation must be equal or higher than 6 points Age ≥ 18 and ≤ 85 years Occlusion (TICI 0 to 1) of the intracranial internal carotid artery (distal ICA or T occlusions), MCA-M1 segment or tandem proximal ICA/MCA-M1 suitable for endovascular treatment, as evidenced by computed tomography angiogram, magnetic resonance angiogram or angiogram, with or without concomitant cervical carotid occlusion or stenosis Hypodensity on CT or restricted diffusion amounting to an ASPECTS of < 7 on non-contrast CT or < 6 on DWI MRI. Patients 81 to 85 years old with ASPECTS on non-contrast CT or DWI MRI < 9 were excluded. ASPECTS must be evaluated by cerebral blood volume maps of CT perfusion, CTA source imaging (CTA-SI), or DWI-MR in patients whose vascular occlusion study (CTA/MRA) confirming qualifying occlusion is performed beyond 4.5 hours of last seen well.
Interventions	Endovascular thrombectomy with the Solitaire stent retriever and medical therapy (including intravenous alteplase when eligible) versus medical treatment alone. Study sites had to perform more than

REVASCAT 2015 *(Continued)*

	60 mechanical thrombectomy procedures annually to be eligible, and the neurointerventionalists must have performed more than 20 thrombectomies with the Solitaire device.
Outcomes	modified Rankin Scale score 0 to 2 at 90 days follow-up
Funding source	Fundació Ictus Malaltia Vascular through an unrestricted grant from Covidien and others
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Real-time computerised randomisation stratified according to age, baseline NIHSS, therapeutic window, occlusion site, and participating centre
Allocation concealment (selection bias)	Low risk	Real-time, central computerised randomisation stratified according to age, baseline NIHSS, therapeutic window, occlusion site, and participating centre. Done after recruitment to trial.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant lost to follow-up (withdrew consent)
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses
Other bias	Low risk	Trial was terminated early because of lack of equipoise after positive results from other similar trials at 206 randomised participants.

SWIFT PRIME 2015

Study characteristics

Methods	RCT
Participants	Age 18 to 80 years Clinical signs consistent with acute ischaemic stroke NIHSS scores ≥ 8 and < 30 at the time of randomisation Initiation of IV-tPA within 4.5 hours of onset of stroke symptoms (onset time is defined as the last time when the patient was witnessed to be at baseline), with investigator verification that the patient has received/is receiving the correct IV-tPA dose for the estimated weight prior to randomisation TICI 0 to 1 flow in the intracranial internal carotid artery, M1 segment of the MCA, or carotid terminus confirmed by CT or MR angiography that is accessible to the Solitaire FR Device Patient can be treated within 6 hours of onset of stroke symptoms and within 1.5 hours (90 minutes) from CTA or MRA to groin puncture Baseline non-contrast CT or DWI MRI evidence of a small core defined as early ischaemic changes of ASPECTS ≥ 6 Anterior circulation stroke on CTA or MRA

SWIFT PRIME 2015 *(Continued)*

Interventions	Intravenous alteplase followed by endovascular thrombectomy with the use of Solitaire FR or Solitaire 2 device versus intravenous alteplase and best medical treatment alone
Outcomes	modified Rankin Scale score 0 to 2 at 90 days follow-up
Funding source	Covidien
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a minimisation algorithm for investigational site, stroke severity, age, and occlusion location
Allocation concealment (selection bias)	Low risk	Quote from protocol: "At the time of randomization, the site will access IVRS and enter subject's NHSS, age and occlusion location. Based on the information provided, the system will automatically generate the assigned treatment".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses
Other bias	Low risk	Trial was terminated early because of efficacy after 196 participants.

THERAPY 2016

Study characteristics	
Methods	Randomised, multicentre, open-label, controlled phase III, treatment trial
Participants	Age 18 to 85 years Presenting symptoms consistent with an acute ischaemic stroke and eligible for IV r-tPA therapy (patients presenting 3 to 4.5 hours from symptom onset are not eligible if they are > 80 years of age, have a history of stroke and diabetes, anticoagulant use (even if INR is < 1.7), and have an NIHSS score > 25) Evidence of a large vessel occlusion in the anterior circulation with a clot length of 8 mm or longer NIHSS score 8 or greater or aphasic at presentation Signed informed consent
Interventions	Intravenous alteplase alone versus thrombectomy using mainly the Penumbra System and intravenous alteplase. In the intervention group, traditional separator-based aspiration system (Penumbra) was used in 30 participants (54%), the Separator 3D in 14 participants (25%), the ACE catheter (Penumbra) in 15 participants (27%), and either a Solitaire Covidien or Trevo Stryker in 7 participants (13%).
Outcomes	modified Rankin Scale score 0 to 2 at 90 days follow-up

THERAPY 2016 *(Continued)*

Funding source	No specific grant from funding agencies in the public, commercial, or not-for-profit sectors
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Performed by centralised interactive voice response system. Stratified according to enrolling centre
Allocation concealment (selection bias)	Low risk	Performed by centralised interactive voice response system. Stratified according to enrolling centre
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Outcome assessment was performed by blinded, trained, certified investigators and assessed by independent blinded adjudicators.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12 participants were lost to follow-up. Intention-to-treat analysis provided.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Low risk	Trial enrolment was halted by steering committee after results from MR CLEAN.

THRACE 2016

Study characteristics	
Methods	Randomised multicentre clinical trial
Participants	Acute ischaemic stroke, NIHSS 11 to 24 Onset to randomisation within 3 hours Occlusion of the intracranial carotid, the MCA (M1) or the upper third of the basilar artery
Interventions	Standard intravenous thrombolysis with alteplase followed by mechanical thrombectomy in the treatment group versus standard intravenous thrombolysis with alteplase alone in the control group. In the treatment group, a complementary intra-arterial injection of a maximum of 0.3 mg/kg of alteplase at the end of thrombectomy was authorised only in cases of persistent distal occlusions. The neurointerventionalist had to choose a device from the trial's regularly updated list of thrombectomy devices and had to show proof of performance of at least 5 procedures with the chosen device before using it in the trial.
Outcomes	Primary outcome: modified Rankin Scale score at 90 days Secondary outcomes: quality of life (EuroQoL 5-Dimension (EQ-5D)) at 90 days, Barthel Index score at 90 days
Funding source	French Ministry of Health
Notes	Trial was terminated due to efficacy.

THRACE 2016 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by computer analyst masked to centre and participants with the help of a computer-generated sequence and stratified by centre and sequential minimisation to avoid imbalance.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was done at the coordination centre by a computer analyst who was masked to the investigation centres and to the patients".
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Experienced independent interventional neuroradiologists who were masked to participant clinical outcome and other imaging assessed the angiograms before and after thrombectomy. Clinical assessments were made by vascular neurologists not masked to the treatment allocated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 participants lost to follow-up and with missing data were excluded from analysis (modified intention-to-treat analysis).
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Low risk	Trial Steering Committee terminated trial early after 414 participants because of efficacy.

AHA: American Heart Association
APTT: activated partial thromboplastin time
ASPECTS: Alberta Stroke Program Early CT Score
CT: computed tomography
IA: intra-arterial
INR: international normalised ratio
IU: international units
IV-tPA: intravenous tissue plasminogen activator
MCA: middle cerebral artery
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
RCT: randomised controlled trial
rpro-UK: recombinant pro-urokinase
r-tPA: recombinant tissue plasminogen activator
sICH: symptomatic intracerebral haemorrhage
TICI: thrombolysis in cerebral infarction
TIMI: thrombolysis in myocardial infarction
tPA: tissue plasminogen activator
UK: urokinase

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ducrocq 2005	This is not a comparison of IA-tPA versus control, since only the control group is given IV-tPA.

Study	Reason for exclusion
Keris 2001	This is not a comparison of IA-tPA versus control, since the intervention group received both IV-tPA and IA-tPA.
Lewandowski 1999	This is not a comparison of IA-tPA versus control (no IA-tPA), since both groups received IA-tPA. The control group was given IA-tPA, which is not the protocol definition of 'routine medical treatment'.
Sen 2009	This is not a comparison of IA-tPA versus control, since only the control group is given IV-tPA.
SYNTHESIS Expansion 2013	This is not a comparison of IA-tPA versus control, since only the control group is given IV-tPA.
SYNTHESIS pilot 2010	This is not a comparison of IA-tPA versus control, since only the control group is given IV-tPA.
Wolfe 2008	This is not a comparison of IA-tPA versus control (no IA-tPA), since both groups received IA-tPA. The control group was given IA-tPA, which is not the protocol definition of 'routine medical treatment'.

IA-tPA: intra-arterial tissue plasminogen activator
IV-tPA: intravenous tissue plasminogen activator

Characteristics of ongoing studies *[ordered by study ID]*

ISRCTN19922220

Study name	Endovascular treatment of acute stroke for late arrivals
Methods	Multicentre, randomised treatment allocation, open-label treatment and blinded endpoint evaluation
Participants	Patients with acute ischaemic stroke, intracerebral haemorrhage ruled out with non-contrast CT, a confirmed intracranial anterior circulation occlusion and poor-to-good collaterals on CTA will be included. Treatment should be started between 6 and 24 hours after symptom onset. Age should be 18 or over and NIHSS 2 or more.
Interventions	Endovascular treatment versus no endovascular treatment. The treatment is provided in addition to best medical management.
Outcomes	The primary outcome is the score on the modified Rankin Scale at 90 days after inclusion.
Starting date	December 2017
Contact information	late.trialoffice@mumc.nl
Notes	

NCT01717755

Study name	Basilar Artery International Cooperation Study
Methods	Randomised, multicentre, open-label, controlled phase III, treatment trial

NCT01717755 *(Continued)*

Participants	Patients aged 18 years and older with CTA- or MRA-confirmed basilar occlusion
Interventions	Patients will be randomised between best medical management with additional intra-arterial therapy versus best medical management alone. Intra-arterial therapy has to be initiated within 6 hours from estimated time of basilar artery occlusion. If used as part of best medical management, intravenous thrombolytic treatment should be started within 4.5 hours of estimated time of stroke onset.
Outcomes	Favourable outcome at day 90 defined as mRS - functional scale of 0 to 3
Starting date	23 October 2012
Contact information	WJ Schonewille, St Antonius Hospital Nieuwegein w.schonewille@antoniusziekenhuis.nl
Notes	

NCT01852201

Study name	PerfusiOn imaging Selection of Ischemic sTroke patIents for endoVascular thErapy (POSITIVE)
Methods	Randomised, multicentre, open-label, controlled phase III, treatment trial
Participants	Age 18 and older (i.e. candidates must have had their 18th birthday) NIHSS ≥ 8 at the time of neuroimaging. Presenting or persistent symptoms within 6 to 12 hours of when groin puncture can be obtained Neuroimaging demonstrates large vessel proximal occlusion (distal Internal Carotid Artery through MCA M1 bifurcation) The operator feels that the stroke can be appropriately treated with traditional endovascular techniques (endovascular mechanical thrombectomy without adjunctive devices such as stents) Patients who are within 6 to 12 hours of symptom onset and who have received IV-tPA without symptom improvement are eligible for this study. Patients presenting earlier than 6 hours should be treated according to local standard of care.
Interventions	Best medical therapy vs intra-arterial treatment plus best medical therapy
Outcomes	modified Rankin Scale score 0 to 2 at 90 days follow-up
Starting date	September 2013
Contact information	Adrian Parker, Medical University of South Carolina, USA parkerad@musc.edu
Notes	

NCT02419781

Study name	Recovery by endovascular salvage for cerebral ultra-acute embolism
Methods	Randomised, open-label, controlled trial
Participants	Acute ischaemic stroke patients who were treated with intravenous r-tPA therapy within 4.5 hours from onset and have persistent occlusion of proximal internal carotid or middle cerebral artery confirmed by cerebral angiography Patients who can receive endovascular treatment within 8 hours after the onset Patients whose DWI-ASPECTS was 5 points and more, or CT-ASPECT was 6 points and more just before cerebral angiography Patients whose NIHSS is between 8 and 29 points Patients who are between 20 and 85 years of age
Interventions	Best medical therapy vs intra-arterial treatment plus best medical therapy
Outcomes	Assessment of modified Rankin Scale shift analysis at 90 days after onset
Starting date	October 2014
Contact information	Shinichi Yoshimura, Hyogo College of Medicine rescue-j@hyo-med.ac.jp
Notes	

NCT03094715

Study name	Efficacy and safety of thrombectomy in stroke with extended lesion and extended time window (TENSION)
Methods	Prospective, open-label, blinded endpoint, randomised controlled trial
Participants	Randomisation within 11 hours after stroke onset (if known) or last seen well Endovascular treatment is expected to be finished within 12 hours after known symptom onset or last seen well by judgement of the interventional neuroradiologist in charge (if stroke onset is known) Patient must demonstrate clinical signs and symptoms attributable to target area of occlusion consistent with the diagnosis of ischaemic stroke, including impairment of the following: language, motor function, sensation, cognition, gaze, and/or vision for at least 30 minutes without relevant improvement Men and women above 18 years of age NIHSS score < 2 Prior to new focal neurological deficit, mRS score was ≤ 2
Interventions	Best medical treatment vs endovascular thrombectomy and best medical care
Outcomes	Clinical outcome: modified Rankin Scale at 90 days
Starting date	March 2017
Contact information	Susanne Bonekamp, DVM, PhD

NCT03094715 *(Continued)*

	susanne.bonekamp@med.uni-heidelberg.de
Notes	

NCT03805308

Study name	The TESLA Trial: Thrombectomy for Emergent Salvage of Large Anterior circulation ischemic stroke
Methods	Prospective, randomised, open-label, blinded endpoint trial
Participants	Patient presenting with symptoms consistent with an acute ischaemic stroke Age 18 to 85 years Imaging evidence of an anterior circulation occlusion of the internal carotid artery terminus or MCA main stem (MCA M1) segment, or both NIHSS score > 6 at the time of randomisation Ability to randomise within 24 hours of stroke onset Pre-stroke mRS score 0 to 1
Interventions	Medical management vs intra-arterial therapy
Outcomes	Utility-weighted 90-day modified Rankin Scale score
Starting date	January 2019
Contact information	Mary S Patterson, MS mspatterson@mercy.com
Notes	

ASPECTS: Alberta Stroke Program Early CT Score
CT: computed tomography
CTA: computed tomography angiography
DWI: diffusion-weighted imaging
IV: intravenous
IV-tPA: intravenous tissue plasminogen activator
MCA: middle cerebral artery
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
r-tPA: recombinant tissue plasminogen activator
sICH: symptomatic intracerebral haemorrhage
TCD: transcranial Doppler
tPA: tissue plasminogen activator

DATA AND ANALYSES

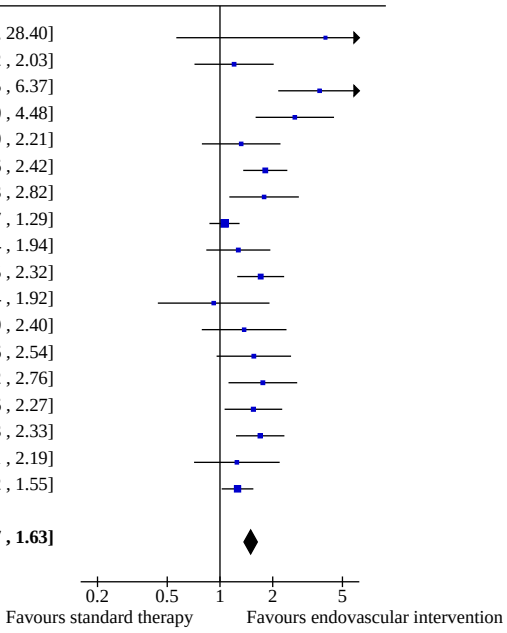
Comparison 1. Favourable functional outcome at end of follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Functional outcome: mRS 0 to 2	18	3715	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.37, 1.63]
1.2 Functional outcome: mRS 0 to 1	18	3632	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.42, 1.82]

Analysis 1.1. Comparison 1: Favourable functional outcome at end of follow-up, Outcome 1: Functional outcome: mRS 0 to 2

	Experimental		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
AUST 2005	4	8	1	8	0.2%	4.00 [0.56 , 28.40]	
BEST 2019	22	66	18	65	3.4%	1.20 [0.72 , 2.03]	
DAWN 2018	52	107	13	99	2.5%	3.70 [2.15 , 6.37]	
DEFUSE 2018	41	92	15	90	2.8%	2.67 [1.60 , 4.48]	
EASI 2017	20	40	14	37	2.7%	1.32 [0.79 , 2.21]	
ESCAPE 2015	87	164	43	147	8.5%	1.81 [1.36 , 2.42]	
EXTEND-IA 2015	25	35	14	35	2.6%	1.79 [1.13 , 2.82]	
IMS III 2013	177	415	86	214	21.3%	1.06 [0.87 , 1.29]	
MELT 2007	28	57	22	57	4.1%	1.27 [0.84 , 1.94]	
MR CLEAN 2015	76	233	51	267	8.9%	1.71 [1.25 , 2.32]	
MR RESCUE 2013	12	64	11	54	2.2%	0.92 [0.44 , 1.92]	
PISTE 2016	17	33	12	32	2.3%	1.37 [0.79 , 2.40]	
PROACT 2 1999	48	121	15	59	3.8%	1.56 [0.96 , 2.54]	
RESILIENT 2020	39	111	22	110	4.1%	1.76 [1.12 , 2.76]	
REVASCAT 2015	45	103	29	103	5.4%	1.55 [1.06 , 2.27]	
SWIFT PRIME 2015	59	98	33	93	6.4%	1.70 [1.23 , 2.33]	
THERAPY 2016	19	50	14	46	2.7%	1.25 [0.71 , 2.19]	
THRACE 2016	106	200	85	202	15.9%	1.26 [1.02 , 1.55]	
Total (95% CI)		**1997**		**1718**	**100.0%**	**1.50 [1.37 , 1.63]**	
Total events:	877		498				

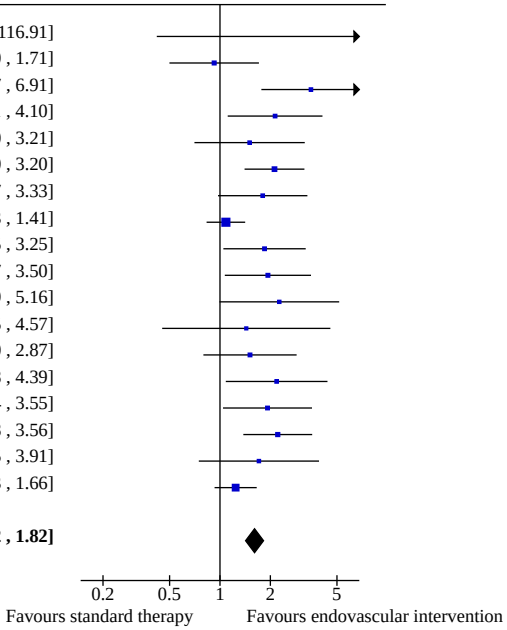
Heterogeneity: Chi² = 38.51, df = 17 (P = 0.002); I² = 56%
Test for overall effect: Z = 9.00 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Favourable functional outcome at end of follow-up, Outcome 2: Functional outcome: mRS 0 to 1

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AUST 2005	3	8	0	8	0.2%	7.00 [0.42 , 116.91]
BEST 2019	15	66	16	65	5.1%	0.92 [0.50 , 1.71]
DAWN 2018	34	107	9	99	3.0%	3.50 [1.77 , 6.91]
DEFUSE 2018	24	92	11	90	3.5%	2.13 [1.11 , 4.10]
EASI 2017	13	40	8	37	2.6%	1.50 [0.70 , 3.21]
ESCAPE 2015	58	160	25	146	8.3%	2.12 [1.40 , 3.20]
EXTEND-IA 2015	18	35	10	35	3.2%	1.80 [0.97 , 3.33]
IMS III 2013	122	415	58	214	24.3%	1.08 [0.83 , 1.41]
MELT 2007	24	57	13	57	4.1%	1.85 [1.05 , 3.25]
MR CLEAN 2015	27	233	16	267	4.7%	1.93 [1.07 , 3.50]
PISTE 2016	14	33	6	32	1.9%	2.26 [0.99 , 5.16]
PROACT 1 1998	8	26	3	14	1.2%	1.44 [0.45 , 4.57]
PROACT 2 1999	31	121	10	59	4.3%	1.51 [0.80 , 2.87]
RESILIENT 2020	22	111	10	110	3.2%	2.18 [1.08 , 4.39]
REVASCAT 2015	25	103	13	103	4.1%	1.92 [1.04 , 3.55]
SWIFT PRIME 2015	42	98	18	93	5.9%	2.21 [1.38 , 3.56]
THERAPY 2016	13	50	7	46	2.3%	1.71 [0.75 , 3.91]
THRACE 2016	70	200	57	202	18.0%	1.24 [0.93 , 1.66]
Total (95% CI)		**1955**		**1677**	**100.0%**	**1.61 [1.42 , 1.82]**
Total events:	563		290			

Heterogeneity: Chi² = 27.45, df = 17 (P = 0.05); I² = 38%
Test for overall effect: Z = 7.56 (P < 0.00001)
Test for subgroup differences: Not applicable



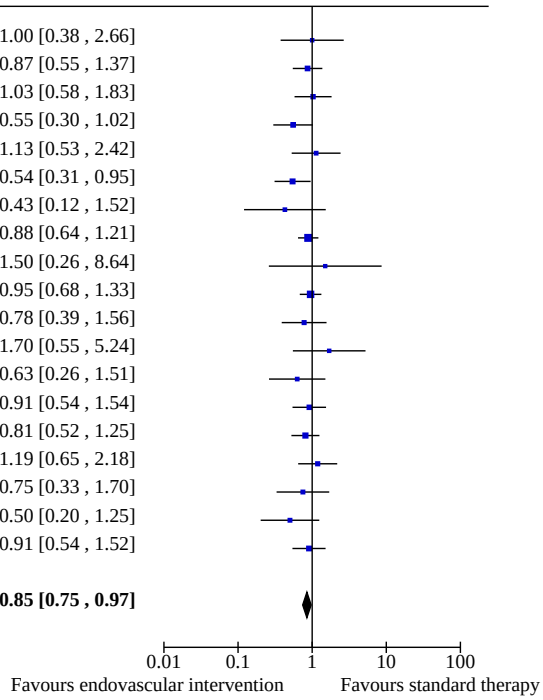
Comparison 2. Death from all causes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Death from all causes at end of follow-up	19	3793	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.75, 0.97]
2.2 Death from all causes within acute phase (first 2 weeks)	3	1243	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.77, 1.47]

Analysis 2.1. Comparison 2: Death from all causes, Outcome 1: Death from all causes at end of follow-up

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AUST 2005	4	8	4	8	1.0%	1.00 [0.38 , 2.66]
BEST 2019	22	66	25	65	6.6%	0.87 [0.55 , 1.37]
DAWN 2018	20	107	18	99	4.9%	1.03 [0.58 , 1.83]
DEFUSE 2018	13	92	23	90	6.1%	0.55 [0.30 , 1.02]
EASI 2017	11	40	9	37	2.4%	1.13 [0.53 , 2.42]
ESCAPE 2015	17	164	28	147	7.7%	0.54 [0.31 , 0.95]
EXTEND-IA 2015	3	35	7	35	1.8%	0.43 [0.12 , 1.52]
IMS III 2013	83	434	48	222	16.5%	0.88 [0.64 , 1.21]
MELT 2007	3	57	2	57	0.5%	1.50 [0.26 , 8.64]
MR CLEAN 2015	49	233	59	267	14.3%	0.95 [0.68 , 1.33]
MR RESCUE 2013	12	64	13	54	3.7%	0.78 [0.39 , 1.56]
PISTE 2016	7	33	4	32	1.1%	1.70 [0.55 , 5.24]
PROACT 1 1998	7	26	6	14	2.0%	0.63 [0.26 , 1.51]
PROACT 2 1999	30	121	16	59	5.6%	0.91 [0.54 , 1.54]
RESILIENT 2020	27	111	33	110	8.6%	0.81 [0.52 , 1.25]
REVASCAT 2015	19	103	16	103	4.2%	1.19 [0.65 , 2.18]
SWIFT PRIME 2015	9	98	12	98	3.1%	0.75 [0.33 , 1.70]
THERAPY 2016	6	50	11	46	3.0%	0.50 [0.20 , 1.25]
THRACE 2016	24	202	27	206	7.0%	0.91 [0.54 , 1.52]
Total (95% CI)		**2044**		**1749**	**100.0%**	**0.85 [0.75 , 0.97]**
Total events:	366		361			

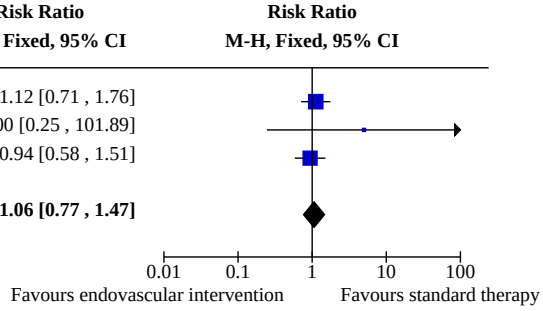
Heterogeneity: Chi² = 12.10, df = 18 (P = 0.84); I² = 0%
Test for overall effect: Z = 2.46 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Death from all causes, Outcome 2: Death from all causes within acute phase (first 2 weeks)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IMS III 2013	52	415	24	214	50.3%	1.12 [0.71 , 1.76]
MELT 2007	2	57	0	57	0.8%	5.00 [0.25 , 101.89]
MR CLEAN 2015	27	233	33	267	48.9%	0.94 [0.58 , 1.51]
Total (95% CI)		**705**		**538**	**100.0%**	**1.06 [0.77 , 1.47]**
Total events:	81		57			

Heterogeneity: Chi² = 1.32, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.72)
Test for subgroup differences: Not applicable



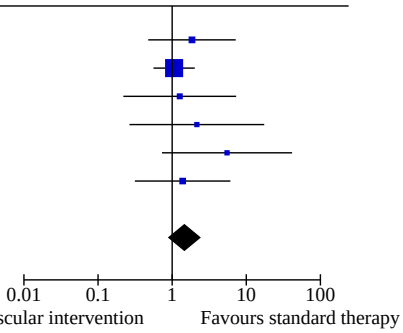
Comparison 3. Symptomatic intracranial haemorrhage (NINDS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Symptomatic intracranial haemorrhage within 24 hours	6	1559	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.91, 2.36]
3.2 Symptomatic intracranial haemorrhage at the end of follow-up	10	1752	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.72, 1.52]

Analysis 3.1. Comparison 3: Symptomatic intracranial haemorrhage (NINDS), Outcome 1: Symptomatic intracranial haemorrhage within 24 hours

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DAWN 2018	6	107	3	99	11.1%	1.85 [0.48 , 7.20]
IMS III 2013	27	434	13	222	61.3%	1.06 [0.56 , 2.02]
MR RESCUE 2013	3	64	2	54	7.7%	1.27 [0.22 , 7.30]
PROACT 1 1998	4	26	1	14	4.6%	2.15 [0.27 , 17.46]
PROACT 2 1999	11	108	1	54	4.8%	5.50 [0.73 , 41.50]
THRACE 2016	4	185	3	192	10.5%	1.38 [0.31 , 6.10]
Total (95% CI)		**924**		**635**	**100.0%**	**1.46 [0.91 , 2.36]**
Total events:	55		23			

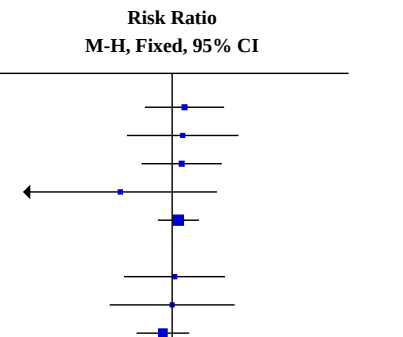
Heterogeneity: Chi² = 2.88, df = 5 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Symptomatic intracranial haemorrhage (NINDS), Outcome 2: Symptomatic intracranial haemorrhage at the end of follow-up

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DEFUSE 2018	6	92	4	90	8.1%	1.47 [0.43 , 5.03]
EASI 2017	3	40	2	37	4.1%	1.39 [0.25 , 7.85]
ESCAPE 2015	6	164	4	147	8.4%	1.34 [0.39 , 4.67]
EXTEND-IA 2015	0	35	2	35	5.0%	0.20 [0.01 , 4.02]
MR CLEAN 2015	18	233	17	267	31.6%	1.21 [0.64 , 2.30]
PISTE 2016	0	33	0	32		Not estimable
PROACT 1 1998	4	26	2	14	5.2%	1.08 [0.22 , 5.17]
REVASCAT 2015	2	103	2	103	4.0%	1.00 [0.14 , 6.96]
SWIFT PRIME 2015	9	98	12	98	23.9%	0.75 [0.33 , 1.70]
THERAPY 2016	4	43	6	62	9.8%	0.96 [0.29 , 3.20]
Total (95% CI)		**867**		**885**	**100.0%**	**1.05 [0.72 , 1.52]**
Total events:	52		51			

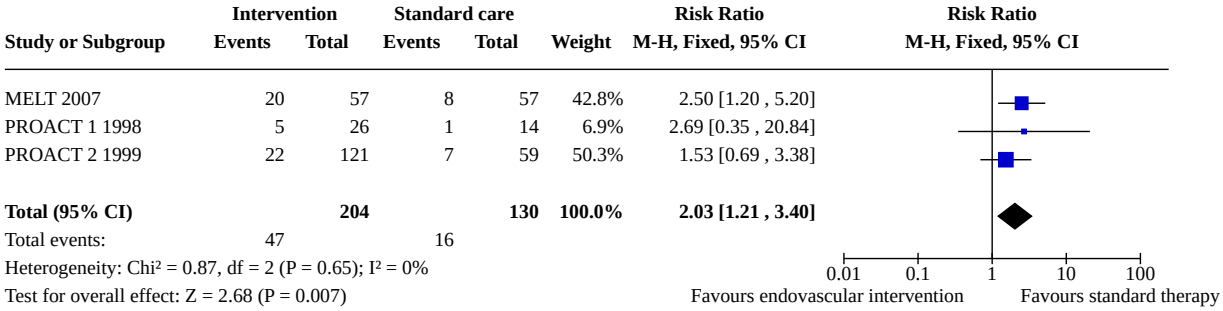
Heterogeneity: Chi² = 2.58, df = 8 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Not applicable



Comparison 4. Neurological outcome at the end of follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Neurological outcome: NIHSS 0 to 1	3	334	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.21, 3.40]

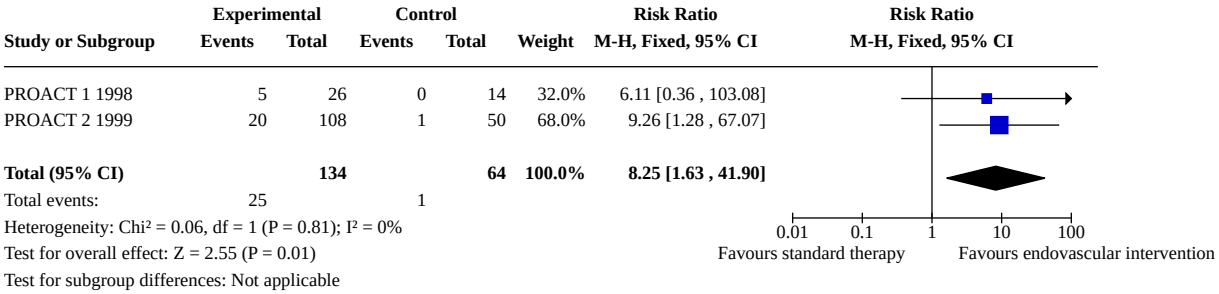
Analysis 4.1. Comparison 4: Neurological outcome at the end of follow-up, Outcome 1: Neurological outcome: NIHSS 0 to 1



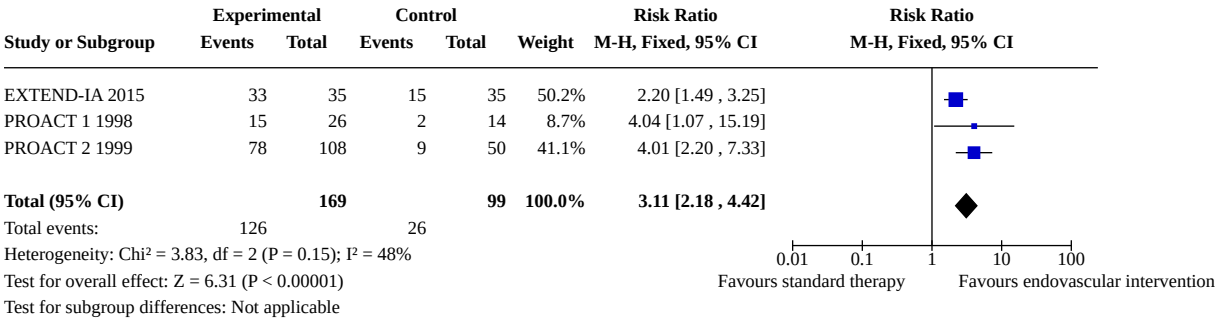
Comparison 5. Degree of recanalisation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Recanalisation: TIMI grade 3	2	198	Risk Ratio (M-H, Fixed, 95% CI)	8.25 [1.63, 41.90]
5.2 Recanalisation: TICI grade 2 and 3	3	268	Risk Ratio (M-H, Fixed, 95% CI)	3.11 [2.18, 4.42]

Analysis 5.1. Comparison 5: Degree of recanalisation, Outcome 1: Recanalisation: TIMI grade 3



Analysis 5.2. Comparison 5: Degree of recanalisation, Outcome 2: Recanalisation: TICI grade 2 and 3



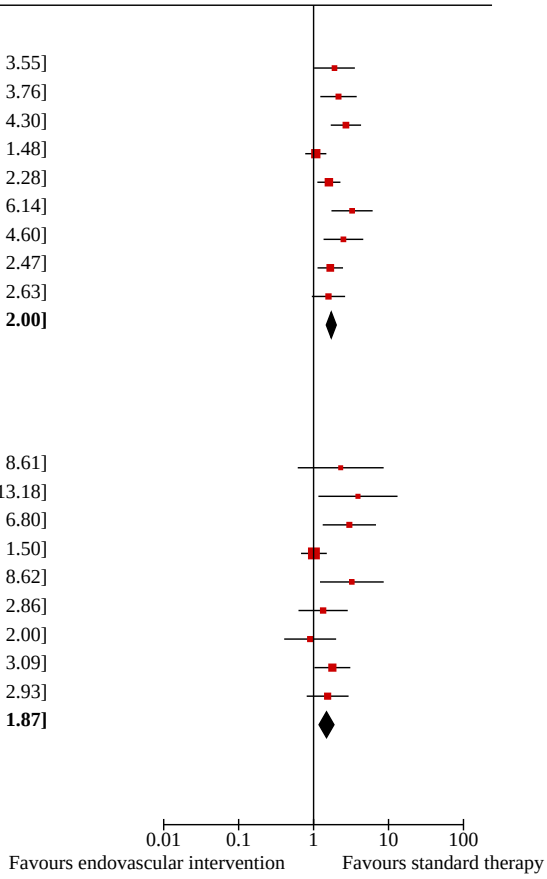
Comparison 6. Subgroup analyses (functional outcome)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Age	9		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.1.1 Younger age	9		Risk Ratio (IV, Fixed, 95% CI)	1.72 [1.48, 2.00]
6.1.2 Older age	9		Risk Ratio (IV, Fixed, 95% CI)	1.49 [1.18, 1.87]
6.2 Sex	7		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.2.1 Men	7		Risk Ratio (IV, Fixed, 95% CI)	1.67 [1.37, 2.04]
6.2.2 Women	7		Risk Ratio (IV, Fixed, 95% CI)	1.63 [1.34, 1.98]
6.3 Stroke severity (NIHSS score)	9		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.3.1 Lower NIHSS score	9		Risk Ratio (IV, Fixed, 95% CI)	1.42 [1.22, 1.66]
6.3.2 Higher NIHSS score	9		Risk Ratio (IV, Fixed, 95% CI)	2.00 [1.57, 2.55]
6.4 Early ischaemic changes on CT according to the Alberta Stroke Program Early CT Score (ASPECTS)	6		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.4.1 Lower ASPECT score	6		Risk Ratio (IV, Fixed, 95% CI)	2.01 [1.53, 2.66]
6.4.2 Higher ASPECT score	6		Risk Ratio (IV, Fixed, 95% CI)	1.39 [1.19, 1.62]
6.5 Mean time to groin puncture or initiation of intra-arterial treatment	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.5.1 Shorter (< 250 minutes)	4	686	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.40, 2.00]
6.5.2 Medium (250 to 300 minutes)	3	1335	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.11, 1.51]
6.5.3 Longer (> 300 minutes)	4	354	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.97, 2.04]
6.6 Intravenous thrombolytic medication	4		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.6.1 Given	4		Risk Ratio (IV, Fixed, 95% CI)	1.95 [1.55, 2.46]
6.6.2 Not given	4		Risk Ratio (IV, Fixed, 95% CI)	2.18 [1.37, 3.47]
6.7 Types of endovascular treatments	17		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.7.1 Trials with participants treated with intra-arterial treatment alone	4	350	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.08, 1.99]
6.7.2 Trials with a majority of participants treated with first-generation mechanical devices	2	747	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.87, 1.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.7.3 Trials with a majority of participants treated with stent retrievers	11	2160	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.59, 2.04]
6.8 Localisation of cerebral artery occlusion	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.8.1 Trials that included both proximal and non-proximal strokes	6	1097	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.99, 1.37]
6.8.2 Trials of that only included proximal occlusion strokes	5	1278	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.47, 1.99]
6.9 Location of occlusion	6		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.9.1 Internal carotid artery	6		Risk Ratio (IV, Fixed, 95% CI)	2.61 [1.88, 3.64]
6.9.2 M1	5		Risk Ratio (IV, Fixed, 95% CI)	1.65 [1.33, 2.04]
6.9.3 M2	1		Risk Ratio (IV, Fixed, 95% CI)	1.35 [0.41, 4.41]
6.10 Penumbra imaging in selecting patients to treatment	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.10.1 Used	3	379	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.22, 2.00]
6.10.2 Not used	8	1996	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.25, 1.59]

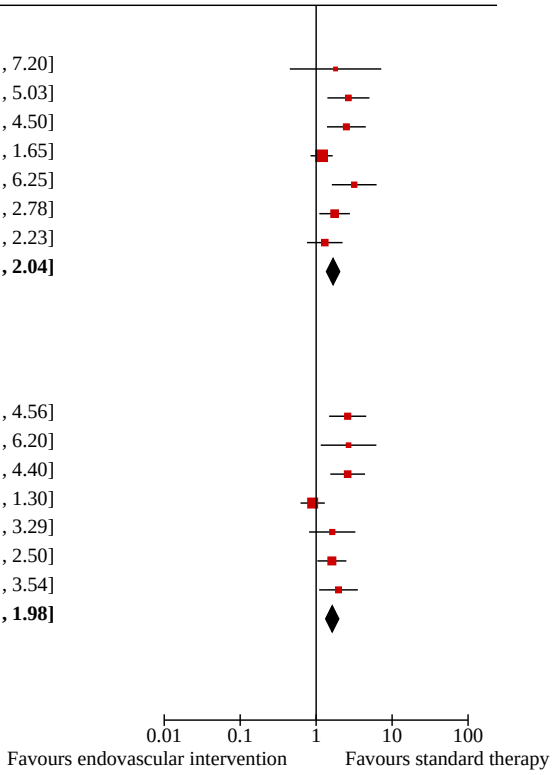
Analysis 6.1. Comparison 6: Subgroup analyses (functional outcome), Outcome 1: Age

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
6.1.1 Younger age				
DAWN 2018	0.64185389	0.31958239	5.9%	1.90 [1.02 , 3.55]
DEFUSE 2018	0.76546784	0.28505224	7.4%	2.15 [1.23 , 3.76]
ESCAPE 2015	0.99325177	0.237430229	10.6%	2.70 [1.70 , 4.30]
IMS III 2013	0.06765865	0.16550175	21.9%	1.07 [0.77 , 1.48]
MR CLEAN 2015	0.47000363	0.180699905	18.4%	1.60 [1.12 , 2.28]
RESILIENT 2020	1.1817272	0.32272279	5.8%	3.26 [1.73 , 6.14]
REVASCAT 2015	0.91629073	0.311104883	6.2%	2.50 [1.36 , 4.60]
SWIFT PRIME 2015	0.51282363	0.199691084	15.0%	1.67 [1.13 , 2.47]
THRACE 2016	0.45742485	0.26073271	8.8%	1.58 [0.95 , 2.63]
Subtotal (95% CI)			**100.0%**	**1.72 [1.48 , 2.00]**
Heterogeneity: Chi² = 18.20, df = 8 (P = 0.02); I² = 56%				
Test for overall effect: Z = 7.02 (P < 0.00001)				
6.1.2 Older age				
DAWN 2018	0.83290912	0.67322891	3.0%	2.30 [0.61 , 8.61]
DEFUSE 2018	1.36353737	0.62009473	3.5%	3.91 [1.16 , 13.18]
ESCAPE 2015	1.0986	0.4175	7.8%	3.00 [1.32 , 6.80]
IMS III 2013	0.00995033	0.20179325	33.3%	1.01 [0.68 , 1.50]
MR CLEAN 2015	1.17557333	0.49924069	5.4%	3.24 [1.22 , 8.62]
RESILIENT 2020	0.29266961	0.38593293	9.1%	1.34 [0.63 , 2.86]
REVASCAT 2015	-0.10536	0.407	8.2%	0.90 [0.41 , 2.00]
SWIFT PRIME 2015	0.57661336	0.281407003	17.1%	1.78 [1.03 , 3.09]
THRACE 2016	0.43178242	0.32799068	12.6%	1.54 [0.81 , 2.93]
Subtotal (95% CI)			**100.0%**	**1.49 [1.18 , 1.87]**
Heterogeneity: Chi² = 13.80, df = 8 (P = 0.09); I² = 42%				
Test for overall effect: Z = 3.41 (P = 0.0007)				
Test for subgroup differences: Chi² = 1.10, df = 1 (P = 0.29), I² = 9.2%				



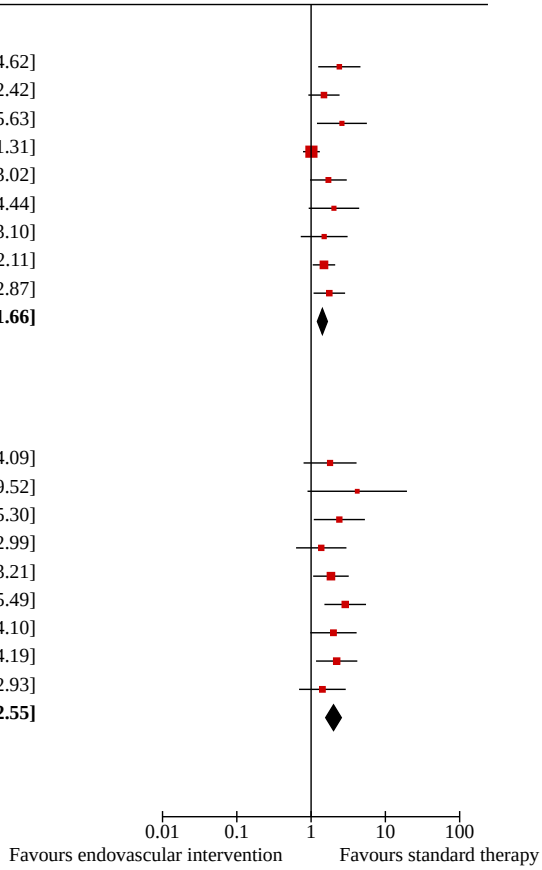
Analysis 6.2. Comparison 6: Subgroup analyses (functional outcome), Outcome 2: Sex

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
6.2.1 Men				
DAWN 2018	0.58778666	0.70729304	2.1%	1.80 [0.45 , 7.20]
DEFUSE 2018	0.97832612	0.32495316	9.8%	2.66 [1.41 , 5.03]
ESCAPE 2015	0.91629073	0.29989116	11.5%	2.50 [1.39 , 4.50]
IMS III 2013	0.16551444	0.17105145	35.5%	1.18 [0.84 , 1.65]
RESILIENT 2020	1.15373159	0.34600696	8.7%	3.17 [1.61 , 6.25]
SWIFT PRIME 2015	0.55961579	0.23614038	18.6%	1.75 [1.10 , 2.78]
THRACE 2016	0.26236426	0.27460164	13.8%	1.30 [0.76 , 2.23]
Subtotal (95% CI)			**100.0%**	**1.67 [1.37 , 2.04]**
Heterogeneity: Chi² = 12.30, df = 6 (P = 0.06); I² = 51%				
Test for overall effect: Z = 5.04 (P < 0.00001)				
6.2.2 Women				
DAWN 2018	0.95551145	0.28671686	12.3%	2.60 [1.48 , 4.56]
DEFUSE 2018	0.98207847	0.43020381	5.5%	2.67 [1.15 , 6.20]
ESCAPE 2015	0.95551145	0.26841484	14.1%	2.60 [1.54 , 4.40]
IMS III 2013	-0.10536052	0.18761468	28.8%	0.90 [0.62 , 1.30]
RESILIENT 2020	0.48858001	0.35755321	7.9%	1.63 [0.81 , 3.29]
SWIFT PRIME 2015	0.47623418	0.22451865	20.1%	1.61 [1.04 , 2.50]
THRACE 2016	0.67803354	0.2988871	11.3%	1.97 [1.10 , 3.54]
Subtotal (95% CI)			**100.0%**	**1.63 [1.34 , 1.98]**
Heterogeneity: Chi² = 17.42, df = 6 (P = 0.008); I² = 66%				
Test for overall effect: Z = 4.84 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%				



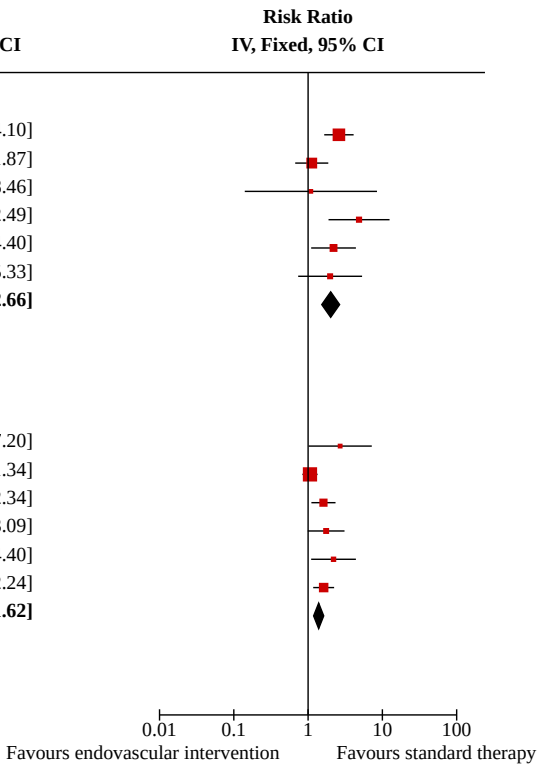
Analysis 6.3. Comparison 6: Subgroup analyses (functional outcome), Outcome 3: Stroke severity (NIHSS score)

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
6.3.1 Lower NIHSS score				
DAWN 2018	0.87546874	0.33375837	5.5%	2.40 [1.25 , 4.62]
DEFUSE 2018	0.39877612	0.24672172	10.1%	1.49 [0.92 , 2.42]
ESCAPE 2015	0.95551145	0.394484637	4.0%	2.60 [1.20 , 5.63]
IMS III 2013	0.00995033	0.13269225	35.1%	1.01 [0.78 , 1.31]
MR CLEAN 2015	0.53649337	0.290185439	7.3%	1.71 [0.97 , 3.02]
RESILIENT 2020	0.70803579	0.39935581	3.9%	2.03 [0.93 , 4.44]
REVASCAT 2015	0.40546511	0.370376022	4.5%	1.50 [0.73 , 3.10]
SWIFT PRIME 2015	0.39877612	0.177506034	19.6%	1.49 [1.05 , 2.11]
THRACE 2016	0.56531381	0.24932423	9.9%	1.76 [1.08 , 2.87]
Subtotal (95% CI)			**100.0%**	**1.42 [1.22 , 1.66]**
Heterogeneity: Chi² = 13.50, df = 8 (P = 0.10); I² = 41%				
Test for overall effect: Z = 4.45 (P < 0.00001)				
6.3.2 Higher NIHSS score				
DAWN 2018	0.58778666	0.41893565	8.7%	1.80 [0.79 , 4.09]
DEFUSE 2018	1.43031125	0.78639075	2.5%	4.18 [0.89 , 19.52]
ESCAPE 2015	0.87546874	0.404203104	9.3%	2.40 [1.09 , 5.30]
IMS III 2013	0.31481074	0.39819523	9.6%	1.37 [0.63 , 2.99]
MR CLEAN 2015	0.61518564	0.281165968	19.2%	1.85 [1.07 , 3.21]
RESILIENT 2020	1.05779029	0.32882537	14.0%	2.88 [1.51 , 5.49]
REVASCAT 2015	0.69314718	0.366244792	11.3%	2.00 [0.98 , 4.10]
SWIFT PRIME 2015	0.79299252	0.326381744	14.3%	2.21 [1.17 , 4.19]
THRACE 2016	0.35065687	0.36889441	11.2%	1.42 [0.69 , 2.93]
Subtotal (95% CI)			**100.0%**	**2.00 [1.57 , 2.55]**
Heterogeneity: Chi² = 4.31, df = 8 (P = 0.83); I² = 0%				
Test for overall effect: Z = 5.64 (P < 0.00001)				
Test for subgroup differences: Chi² = 5.58, df = 1 (P = 0.02), I² = 82.1%				



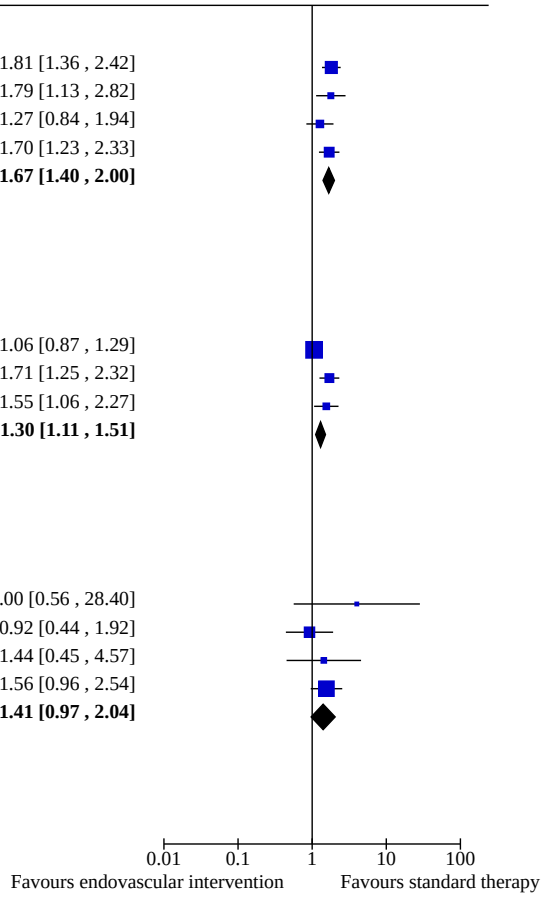
Analysis 6.4. Comparison 6: Subgroup analyses (functional outcome), Outcome 4: Early ischaemic changes on CT according to the Alberta Stroke Program Early CT Score (ASPECTS)

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
6.4.1 Lower ASPECT score				
ESCAPE 2015	0.95551145	0.232385474	36.8%	2.60 [1.65 , 4.10]
IMS III 2013	0.11332869	0.26153558	29.1%	1.12 [0.67 , 1.87]
MR CLEAN 2015	0.0861777	1.045495652	1.8%	1.09 [0.14 , 8.46]
RESILIENT 2020	1.5789787	0.48246218	8.5%	4.85 [1.88 , 12.49]
REVASCAT 2015	0.78845736	0.353646521	15.9%	2.20 [1.10 , 4.40]
SWIFT PRIME 2015	0.68309684	0.505231833	7.8%	1.98 [0.74 , 5.33]
Subtotal (95% CI)			**100.0%**	**2.01 [1.53 , 2.66]**
Heterogeneity: Chi² = 9.97, df = 5 (P = 0.08); I² = 50%				
Test for overall effect: Z = 4.96 (P < 0.00001)				
6.4.2 Higher ASPECT score				
ESCAPE 2015	0.99325177	0.500423088	2.5%	2.70 [1.01 , 7.20]
IMS III 2013	0.05826891	0.1195922	44.3%	1.06 [0.84 , 1.34]
MR CLEAN 2015	0.47623418	0.190773852	17.4%	1.61 [1.11 , 2.34]
RESILIENT 2020	0.55961579	0.29036261	7.5%	1.75 [0.99 , 3.09]
REVASCAT 2015	0.78845736	0.353646521	5.1%	2.20 [1.10 , 4.40]
SWIFT PRIME 2015	0.48242615	0.165331488	23.2%	1.62 [1.17 , 2.24]
Subtotal (95% CI)			**100.0%**	**1.39 [1.19 , 1.62]**
Heterogeneity: Chi² = 10.66, df = 5 (P = 0.06); I² = 53%				
Test for overall effect: Z = 4.12 (P < 0.0001)				
Test for subgroup differences: Chi² = 5.29, df = 1 (P = 0.02), I² = 81.1%				



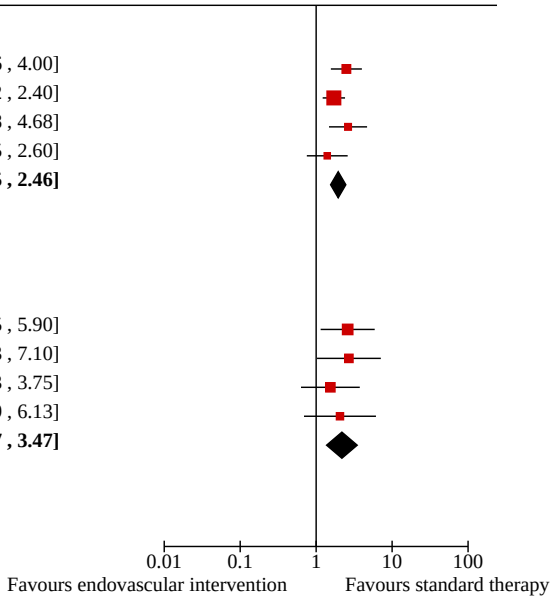
Analysis 6.5. Comparison 6: Subgroup analyses (functional outcome), Outcome 5: Mean time to groin puncture or initiation of intra-arterial treatment

Study or Subgroup	Intervention Events	Intervention Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.5.1 Shorter (< 250 minutes)						
ESCAPE 2015	87	164	43	147	39.4%	1.81 [1.36 , 2.42]
EXTEND-IA 2015	25	35	14	35	12.2%	1.79 [1.13 , 2.82]
MELT 2007	28	57	22	57	19.1%	1.27 [0.84 , 1.94]
SWIFT PRIME 2015	59	98	33	93	29.4%	1.70 [1.23 , 2.33]
Subtotal (95% CI)		**354**		**332**	**100.0%**	**1.67 [1.40 , 2.00]**
Total events:	199		112			
Heterogeneity: Chi² = 2.01, df = 3 (P = 0.57); I² = 0%						
Test for overall effect: Z = 5.71 (P < 0.00001)						
6.5.2 Medium (250 to 300 minutes)						
IMS III 2013	177	415	86	214	59.7%	1.06 [0.87 , 1.29]
MR CLEAN 2015	76	233	51	267	25.0%	1.71 [1.25 , 2.32]
REVASCAT 2015	45	103	29	103	15.3%	1.55 [1.06 , 2.27]
Subtotal (95% CI)		**751**		**584**	**100.0%**	**1.30 [1.11 , 1.51]**
Total events:	298		166			
Heterogeneity: Chi² = 7.87, df = 2 (P = 0.02); I² = 75%						
Test for overall effect: Z = 3.35 (P = 0.0008)						
6.5.3 Longer (> 300 minutes)						
AUST 2005	4	8	1	8	2.7%	4.00 [0.56 , 28.40]
MR RESCUE 2013	12	64	11	54	32.3%	0.92 [0.44 , 1.92]
PROACT 1 1998	8	26	3	14	10.5%	1.44 [0.45 , 4.57]
PROACT 2 1999	48	121	15	59	54.5%	1.56 [0.96 , 2.54]
Subtotal (95% CI)		**219**		**135**	**100.0%**	**1.41 [0.97 , 2.04]**
Total events:	72		30			
Heterogeneity: Chi² = 2.55, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.80 (P = 0.07)						
Test for subgroup differences: Chi² = 4.56, df = 2 (P = 0.10), I² = 56.2%						



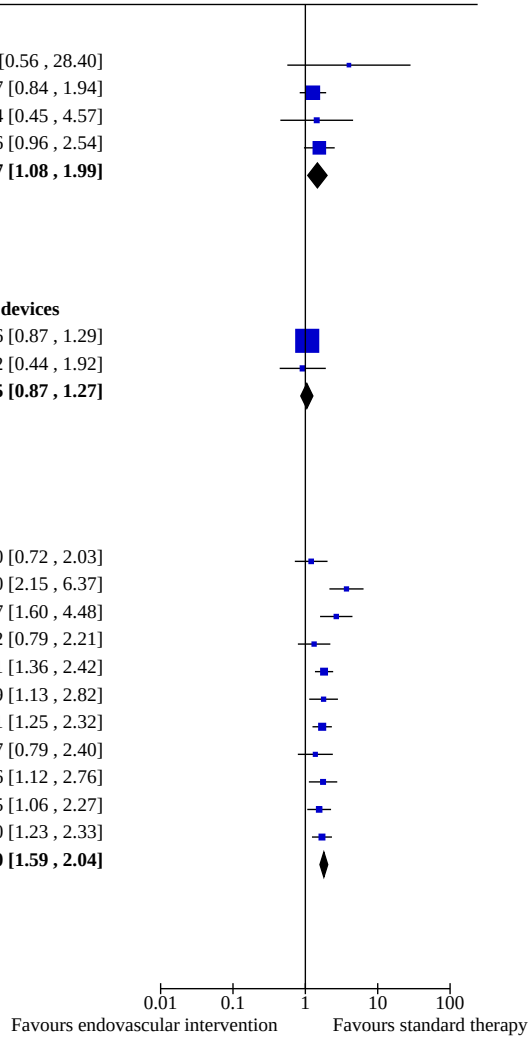
Analysis 6.6. Comparison 6: Subgroup analyses (functional outcome), Outcome 6: Intravenous thrombolytic medication

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
6.6.1 Given				
ESCAPE 2015	0.91629073	0.23979777	24.0%	2.50 [1.56 , 4.00]
MR CLEAN 2015	0.53649337	0.17294662	46.2%	1.71 [1.22 , 2.40]
RESILIENT 2020	0.96698385	0.29423227	16.0%	2.63 [1.48 , 4.68]
REVASCAT 2015	0.33647224	0.3158633	13.8%	1.40 [0.75 , 2.60]
Subtotal (95% CI)			**100.0%**	**1.95 [1.55 , 2.46]**
Heterogeneity: Chi² = 3.78, df = 3 (P = 0.29); I² = 21%				
Test for overall effect: Z = 5.69 (P < 0.00001)				
6.6.2 Not given				
ESCAPE 2015	0.95551145	0.4180821	32.0%	2.60 [1.15 , 5.90]
MR CLEAN 2015	0.99325177	0.49328725	23.0%	2.70 [1.03 , 7.10]
RESILIENT 2020	0.43178242	0.45436762	27.1%	1.54 [0.63 , 3.75]
REVASCAT 2015	0.722270598	0.55637182	18.0%	2.06 [0.69 , 6.13]
Subtotal (95% CI)			**100.0%**	**2.18 [1.37 , 3.47]**
Heterogeneity: Chi² = 0.96, df = 3 (P = 0.81); I² = 0%				
Test for overall effect: Z = 3.30 (P = 0.0010)				
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%				



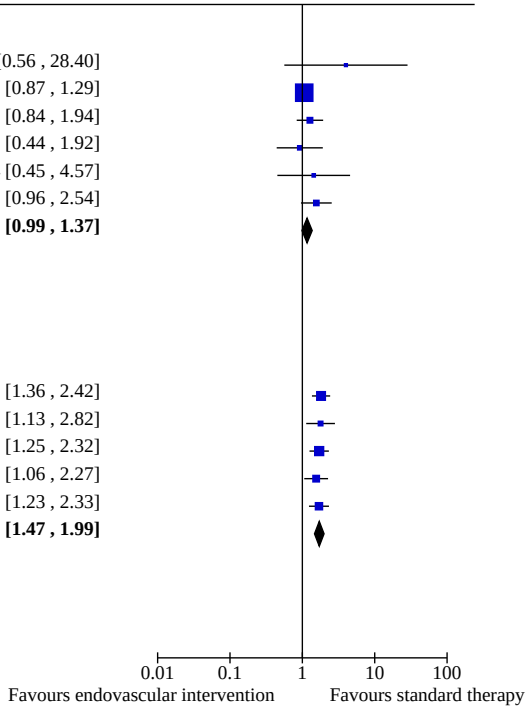
Analysis 6.7. Comparison 6: Subgroup analyses (functional outcome), Outcome 7: Types of endovascular treatments

Study or Subgroup	Intervention Events	Intervention Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.7.1 Trials with participants treated with intra-arterial treatment alone						
AUST 2005	4	8	1	8	2.1%	4.00 [0.56 , 28.40]
MELT 2007	28	57	22	57	46.7%	1.27 [0.84 , 1.94]
PROACT 1 1998	8	26	3	14	8.3%	1.44 [0.45 , 4.57]
PROACT 2 1999	48	121	15	59	42.8%	1.56 [0.96 , 2.54]
Subtotal (95% CI)		**212**		**138**	**100.0%**	**1.47 [1.08 , 1.99]**
Total events:	88		41			
Heterogeneity: Chi² = 1.51, df = 3 (P = 0.68); I² = 0%						
Test for overall effect: Z = 2.45 (P = 0.01)						
6.7.2 Trials with a majority of participants treated with first-generation mechanical devices						
IMS III 2013	177	415	86	214	90.5%	1.06 [0.87 , 1.29]
MR RESCUE 2013	12	64	11	54	9.5%	0.92 [0.44 , 1.92]
Subtotal (95% CI)		**479**		**268**	**100.0%**	**1.05 [0.87 , 1.27]**
Total events:	189		97			
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
6.7.3 Trials with a majority of participants treated with stent retrievers						
BEST 2019	22	66	18	65	6.8%	1.20 [0.72 , 2.03]
DAWN 2018	52	107	13	99	5.1%	3.70 [2.15 , 6.37]
DEFUSE 2018	41	92	15	90	5.7%	2.67 [1.60 , 4.48]
EASI 2017	20	40	14	37	5.5%	1.32 [0.79 , 2.21]
ESCAPE 2015	87	164	43	147	17.1%	1.81 [1.36 , 2.42]
EXTEND-IA 2015	25	35	14	35	5.3%	1.79 [1.13 , 2.82]
MR CLEAN 2015	76	233	51	267	17.9%	1.71 [1.25 , 2.32]
PISTE 2016	17	33	12	32	4.6%	1.37 [0.79 , 2.40]
RESILIENT 2020	39	111	22	110	8.3%	1.76 [1.12 , 2.76]
REVASCAT 2015	45	103	29	103	10.9%	1.55 [1.06 , 2.27]
SWIFT PRIME 2015	59	98	33	93	12.8%	1.70 [1.23 , 2.33]
Subtotal (95% CI)		**1082**		**1078**	**100.0%**	**1.80 [1.59 , 2.04]**
Total events:	483		264			
Heterogeneity: Chi² = 14.48, df = 10 (P = 0.15); I² = 31%						
Test for overall effect: Z = 9.38 (P < 0.00001)						
Test for subgroup differences: Chi² = 21.81, df = 2 (P < 0.0001), I² = 90.8%						



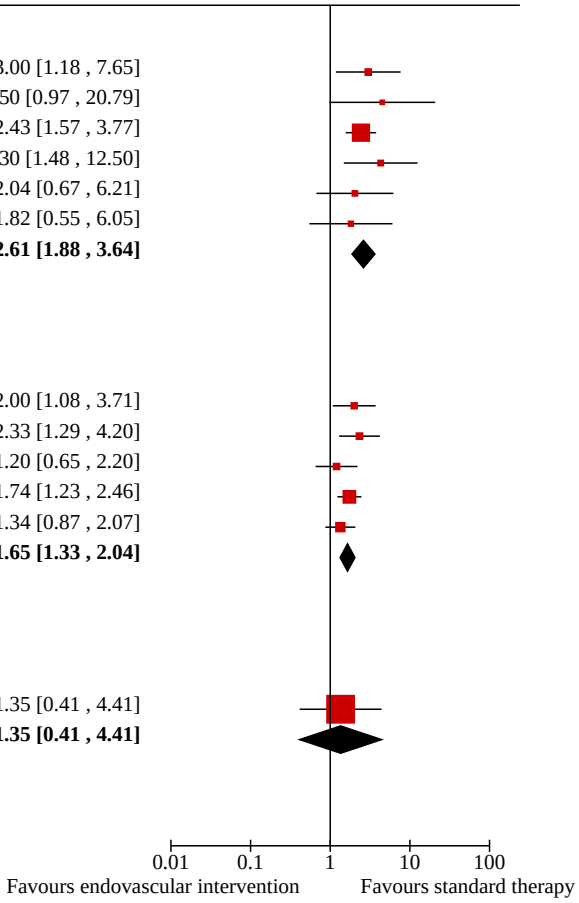
Analysis 6.8. Comparison 6: Subgroup analyses (functional outcome), Outcome 8: Localisation of cerebral artery occlusion

Study or Subgroup	Treatment Events	Treatment Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.8.1 Trials that included both proximal and non-proximal strokes						
AUST 2005	4	8	1	8	0.6%	4.00 [0.56 , 28.40]
IMS III 2013	177	415	86	214	65.8%	1.06 [0.87 , 1.29]
MELT 2007	28	57	22	57	12.8%	1.27 [0.84 , 1.94]
MR RESCUE 2013	12	64	11	54	6.9%	0.92 [0.44 , 1.92]
PROACT 1 1998	8	26	3	14	2.3%	1.44 [0.45 , 4.57]
PROACT 2 1999	48	121	15	59	11.7%	1.56 [0.96 , 2.54]
Subtotal (95% CI)		**691**		**406**	**100.0%**	**1.16 [0.99 , 1.37]**
Total events:	277		138			
Heterogeneity: Chi² = 4.43, df = 5 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.82 (P = 0.07)						
6.8.2 Trials of that only included proximal occlusion strokes						
ESCAPE 2015	87	164	43	147	26.7%	1.81 [1.36 , 2.42]
EXTEND-IA 2015	25	35	14	35	8.2%	1.79 [1.13 , 2.82]
MR CLEAN 2015	76	233	51	267	28.0%	1.71 [1.25 , 2.32]
REVASCAT 2015	45	103	29	103	17.1%	1.55 [1.06 , 2.27]
SWIFT PRIME 2015	59	98	33	93	19.9%	1.70 [1.23 , 2.33]
Subtotal (95% CI)		**633**		**645**	**100.0%**	**1.71 [1.47 , 1.99]**
Total events:	292		170			
Heterogeneity: Chi² = 0.45, df = 4 (P = 0.98); I² = 0%						
Test for overall effect: Z = 6.96 (P < 0.00001)						
Test for subgroup differences: Chi² = 11.72, df = 1 (P = 0.0006), I² = 91.5%						

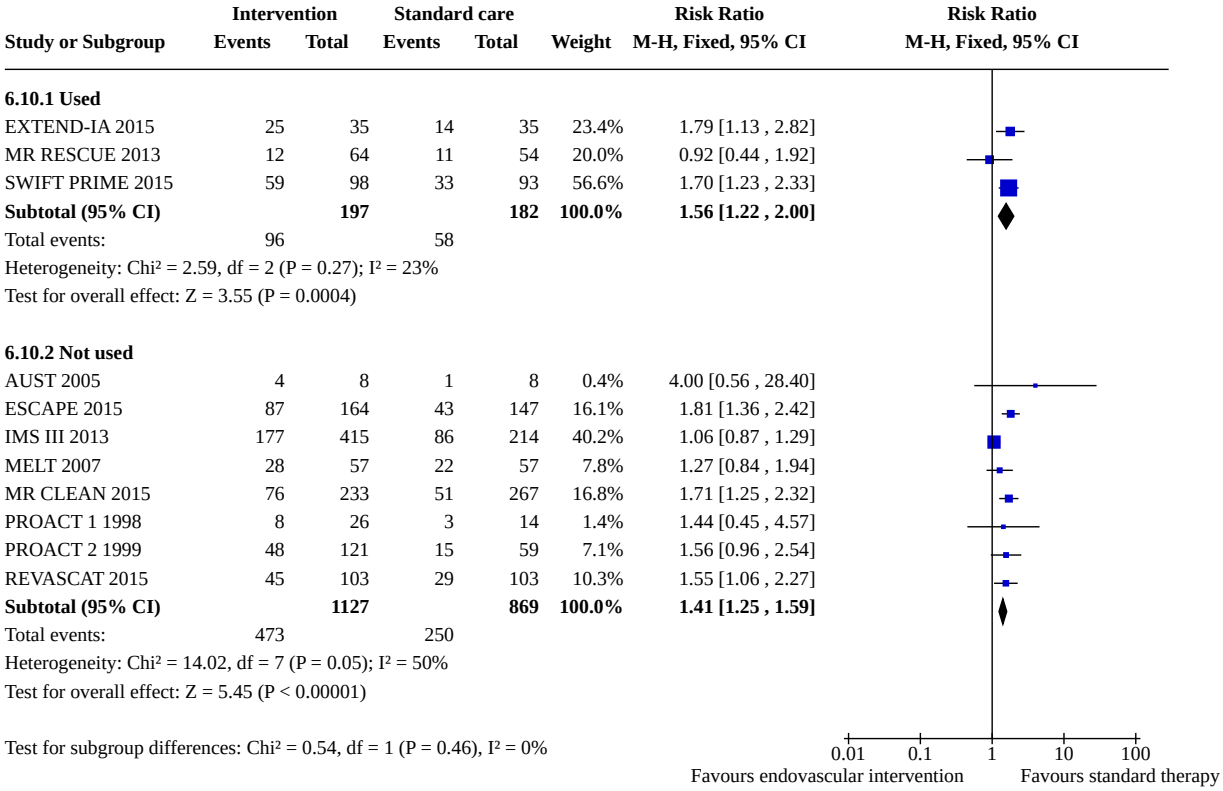


Analysis 6.9. Comparison 6: Subgroup analyses (functional outcome), Outcome 9: Location of occlusion

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
6.9.1 Internal carotid artery				
DAWN 2018	1.09861229	0.47750056	12.5%	3.00 [1.18 , 7.65]
DEFUSE 2018	1.5040774	0.78082467	4.7%	4.50 [0.97 , 20.79]
MR CLEAN 2015	0.88789126	0.224073339	56.8%	2.43 [1.57 , 3.77]
REVASCAT 2015	1.45861502	0.544445725	9.6%	4.30 [1.48 , 12.50]
SWIFT PRIME 2015	0.71294981	0.567964841	8.8%	2.04 [0.67 , 6.21]
THRACE 2016	0.5988365	0.6125499	7.6%	1.82 [0.55 , 6.05]
Subtotal (95% CI)			**100.0%**	**2.61 [1.88 , 3.64]**
Heterogeneity: Chi² = 2.05, df = 5 (P = 0.84); I² = 0%				
Test for overall effect: Z = 5.69 (P < 0.00001)				
6.9.2 M1				
DAWN 2018	0.69314718	0.31550067	12.0%	2.00 [1.08 , 3.71]
DEFUSE 2018	0.845868268	0.30052513	13.2%	2.33 [1.29 , 4.20]
REVASCAT 2015	0.18232156	0.309252961	12.4%	1.20 [0.65 , 2.20]
SWIFT PRIME 2015	0.55388511	0.176671549	38.1%	1.74 [1.23 , 2.46]
THRACE 2016	0.29266961	0.22112517	24.3%	1.34 [0.87 , 2.07]
Subtotal (95% CI)			**100.0%**	**1.65 [1.33 , 2.04]**
Heterogeneity: Chi² = 3.73, df = 4 (P = 0.44); I² = 0%				
Test for overall effect: Z = 4.58 (P < 0.00001)				
6.9.3 M2				
SWIFT PRIME 2015	0.30010459	0.603964335	100.0%	1.35 [0.41 , 4.41]
Subtotal (95% CI)			**100.0%**	**1.35 [0.41 , 4.41]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.50 (P = 0.62)				



Analysis 6.10. Comparison 6: Subgroup analyses (functional outcome), Outcome 10: Penumbra imaging in selecting patients to treatment

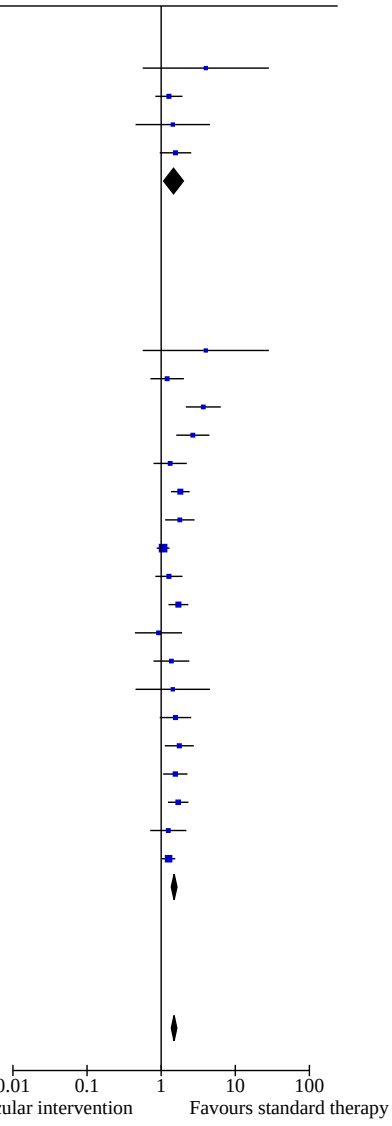


Comparison 7. Sensitivity analyses (functional outcome, mRS 0 to 2, or mRS 0 to 1 if data not available for mRS 0 to 2))

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Trials included in the previous review vs trials included in the current review	19	4105	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.37, 1.62]
7.1.1 Trials included in the previous review	4	350	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.08, 1.99]
7.1.2 Trials included in the current review	19	3755	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.37, 1.63]
7.2 Trials that included all planned participants vs trials stopped early	19	3533	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.40, 1.69]
7.2.1 Trials that included all planned participants	3	798	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.22, 1.98]
7.2.2 Trials stopped early	16	2735	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.39, 1.70]
7.3 Functional outcome: mRS 0 to 2 (random effects)	18	3715	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.33, 1.78]

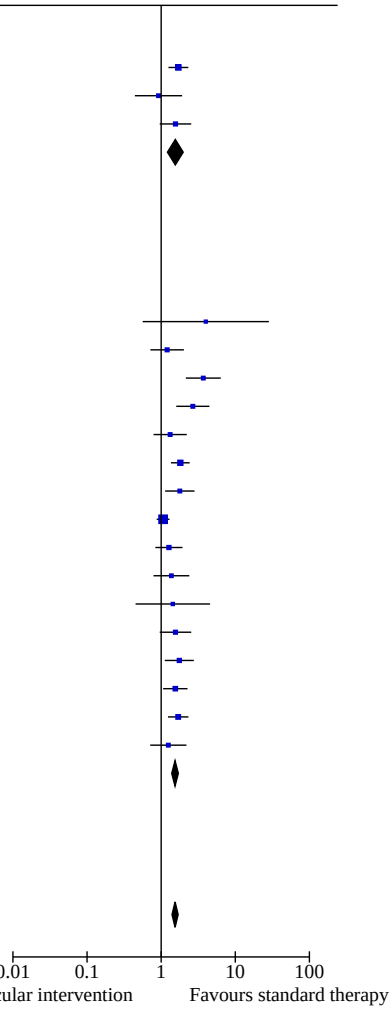
Analysis 7.1. Comparison 7: Sensitivity analyses (functional outcome, mRS 0 to 2, or mRS 0 to 1 if data not available for mRS 0 to 2)), Outcome 1: Trials included in the previous review vs trials included in the current review

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 Trials included in the previous review						
AUST 2005	4	8	1	8	0.2%	4.00 [0.56 , 28.40]
MELT 2007	28	57	22	57	3.8%	1.27 [0.84 , 1.94]
PROACT 1 1998	8	26	3	14	0.7%	1.44 [0.45 , 4.57]
PROACT 2 1999	48	121	15	59	3.5%	1.56 [0.96 , 2.54]
Subtotal (95% CI)		**212**		**138**	**8.1%**	**1.47 [1.08 , 1.99]**
Total events:	88		41			
Heterogeneity: Chi² = 1.51, df = 3 (P = 0.68); I² = 0%						
Test for overall effect: Z = 2.45 (P = 0.01)						
7.1.2 Trials included in the current review						
AUST 2005	4	8	1	8	0.2%	4.00 [0.56 , 28.40]
BEST 2019	22	66	18	65	3.1%	1.20 [0.72 , 2.03]
DAWN 2018	52	107	13	99	2.3%	3.70 [2.15 , 6.37]
DEFUSE 2018	41	92	15	90	2.6%	2.67 [1.60 , 4.48]
EASI 2017	20	40	14	37	2.5%	1.32 [0.79 , 2.21]
ESCAPE 2015	87	164	43	147	7.8%	1.81 [1.36 , 2.42]
EXTEND-IA 2015	25	35	14	35	2.4%	1.79 [1.13 , 2.82]
IMS III 2013	177	415	86	214	19.4%	1.06 [0.87 , 1.29]
MELT 2007	28	57	22	57	3.8%	1.27 [0.84 , 1.94]
MR CLEAN 2015	76	233	51	267	8.1%	1.71 [1.25 , 2.32]
MR RESCUE 2013	12	64	11	54	2.0%	0.92 [0.44 , 1.92]
PISTE 2016	17	33	12	32	2.1%	1.37 [0.79 , 2.40]
PROACT 1 1998	8	26	3	14	0.7%	1.44 [0.45 , 4.57]
PROACT 2 1999	48	121	15	59	3.5%	1.56 [0.96 , 2.54]
RESILIENT 2020	39	111	22	110	3.8%	1.76 [1.12 , 2.76]
REVASCAT 2015	45	103	29	103	5.0%	1.55 [1.06 , 2.27]
SWIFT PRIME 2015	59	98	33	93	5.8%	1.70 [1.23 , 2.33]
THERAPY 2016	19	50	14	46	2.5%	1.25 [0.71 , 2.19]
THRACE 2016	106	200	85	202	14.5%	1.26 [1.02 , 1.55]
Subtotal (95% CI)		**2023**		**1732**	**91.9%**	**1.50 [1.37 , 1.63]**
Total events:	885		501			
Heterogeneity: Chi² = 38.50, df = 18 (P = 0.003); I² = 53%						
Test for overall effect: Z = 9.02 (P < 0.00001)						
Total (95% CI)		**2235**		**1870**	**100.0%**	**1.49 [1.37 , 1.62]**
Total events:	973		542			
Heterogeneity: Chi² = 40.01, df = 22 (P = 0.01); I² = 45%						
Test for overall effect: Z = 9.34 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%						



Analysis 7.2. Comparison 7: Sensitivity analyses (functional outcome, mRS 0 to 2, or mRS 0 to 1 if data not available for mRS 0 to 2)), Outcome 2: Trials that included all planned participants vs trials stopped early

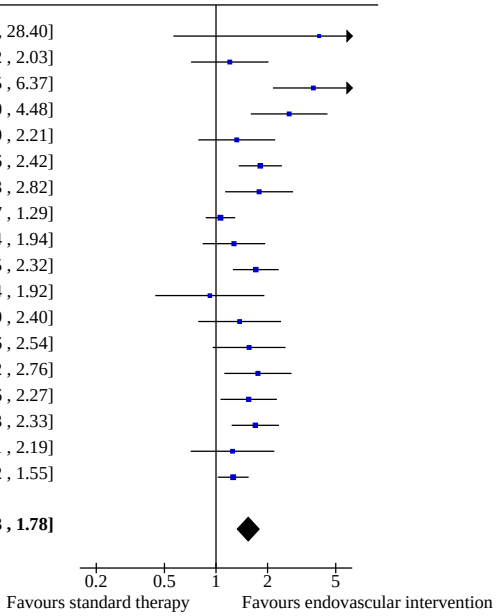
Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 Trials that included all planned participants						
MR CLEAN 2015	76	233	51	267	10.1%	1.71 [1.25 , 2.32]
MR RESCUE 2013	12	64	11	54	2.5%	0.92 [0.44 , 1.92]
PROACT 2 1999	48	121	15	59	4.3%	1.56 [0.96 , 2.54]
Subtotal (95% CI)		**418**		**380**	**16.8%**	**1.55 [1.22 , 1.98]**
Total events:	136		77			
Heterogeneity: Chi² = 2.32, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 3.52 (P = 0.0004)						
7.2.2 Trials stopped early						
AUST 2005	4	8	1	8	0.2%	4.00 [0.56 , 28.40]
BEST 2019	22	66	18	65	3.8%	1.20 [0.72 , 2.03]
DAWN 2018	52	107	13	99	2.9%	3.70 [2.15 , 6.37]
DEFUSE 2018	41	92	15	90	3.2%	2.67 [1.60 , 4.48]
EASI 2017	20	40	14	37	3.1%	1.32 [0.79 , 2.21]
ESCAPE 2015	87	164	43	147	9.6%	1.81 [1.36 , 2.42]
EXTEND-IA 2015	25	35	14	35	3.0%	1.79 [1.13 , 2.82]
IMS III 2013	177	415	86	214	24.0%	1.06 [0.87 , 1.29]
MELT 2007	28	57	22	57	4.7%	1.27 [0.84 , 1.94]
PISTE 2016	17	33	12	32	2.6%	1.37 [0.79 , 2.40]
PROACT 1 1998	8	26	3	14	0.8%	1.44 [0.45 , 4.57]
RESILIENT 2020	48	121	15	59	4.3%	1.56 [0.96 , 2.54]
REVASCAT 2015	39	111	22	110	4.7%	1.76 [1.12 , 2.76]
SWIFT PRIME 2015	45	103	29	103	6.1%	1.55 [1.06 , 2.27]
THERAPY 2016	59	98	33	93	7.2%	1.70 [1.23 , 2.33]
THRACE 2016	19	50	14	46	3.1%	1.25 [0.71 , 2.19]
Subtotal (95% CI)		**1526**		**1209**	**83.2%**	**1.54 [1.39 , 1.70]**
Total events:	691		354			
Heterogeneity: Chi² = 33.92, df = 15 (P = 0.003); I² = 56%						
Test for overall effect: Z = 8.27 (P < 0.00001)						
Total (95% CI)		**1944**		**1589**	**100.0%**	**1.54 [1.40 , 1.69]**
Total events:	827		431			
Heterogeneity: Chi² = 36.29, df = 18 (P = 0.006); I² = 50%						
Test for overall effect: Z = 8.98 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						



Analysis 7.3. Comparison 7: Sensitivity analyses (functional outcome, mRS 0 to 2, or mRS 0 to 1 if data not available for mRS 0 to 2)), Outcome 3: Functional outcome: mRS 0 to 2 (random effects)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AUST 2005	4	8	1	8	0.5%	4.00 [0.56 , 28.40]
BEST 2019	22	66	18	65	4.6%	1.20 [0.72 , 2.03]
DAWN 2018	52	107	13	99	4.4%	3.70 [2.15 , 6.37]
DEFUSE 2018	41	92	15	90	4.7%	2.67 [1.60 , 4.48]
EASI 2017	20	40	14	37	4.7%	1.32 [0.79 , 2.21]
ESCAPE 2015	87	164	43	147	7.9%	1.81 [1.36 , 2.42]
EXTEND-IA 2015	25	35	14	35	5.4%	1.79 [1.13 , 2.82]
IMS III 2013	177	415	86	214	9.5%	1.06 [0.87 , 1.29]
MELT 2007	28	57	22	57	5.8%	1.27 [0.84 , 1.94]
MR CLEAN 2015	76	233	51	267	7.6%	1.71 [1.25 , 2.32]
MR RESCUE 2013	12	64	11	54	2.9%	0.92 [0.44 , 1.92]
PISTE 2016	17	33	12	32	4.3%	1.37 [0.79 , 2.40]
PROACT 2 1999	48	121	15	59	5.0%	1.56 [0.96 , 2.54]
RESILIENT 2020	39	111	22	110	5.4%	1.76 [1.12 , 2.76]
REVASCAT 2015	45	103	29	103	6.4%	1.55 [1.06 , 2.27]
SWIFT PRIME 2015	59	98	33	93	7.4%	1.70 [1.23 , 2.33]
THERAPY 2016	19	50	14	46	4.2%	1.25 [0.71 , 2.19]
THRACE 2016	106	200	85	202	9.3%	1.26 [1.02 , 1.55]
Total (95% CI)		**1997**		**1718**	**100.0%**	**1.54 [1.33 , 1.78]**
Total events:	877		498			

Heterogeneity: Tau² = 0.05; Chi² = 38.51, df = 17 (P = 0.002); I² = 56%
Test for overall effect: Z = 5.85 (P < 0.00001)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. MEDLINE search strategy

The following search strategy was used for MEDLINE (Ovid) and modified for other databases.

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. 1 or 2 or 3
5. radiography, interventional/ or radiology, interventional/
6. catheterization/ or angioplasty/ or angioplasty, balloon/ or angioplasty, balloon, laser-assisted/ or angioplasty, laser/ or atherectomy/ or balloon dilatation/ or catheter ablation/
7. stents/
8. thrombectomy/ or embolectomy/
9. blood vessel prosthesis/ or blood vessel prosthesis implantation/
10. cerebral revascularization/ or reperfusion/ or dilatation/
11. (interventional adj3 (radiolog$ or radiograph$ or neuroradiolog$)).tw.
12. (angioplast$ or stent$).tw.
13. (thrombectomy or thromboaspiration or embolectomy or atherect$).tw.
14. sonothrombolysis.tw.
15. ((mechanical or radiolog$ or pharmacomechanical or laser or endovascular or neurovascular) adj5 (thrombolys$ or reperfusion or fragmentation or aspiration or recanali?ation or clot lys$)).tw.
16. ((clot or thrombus or thrombi or embol$) adj5 (aspirat$ or remov$ or retriev$ or fragmentation or retract$ or extract$ or obliterat$ or dispers$)).tw.
17. ((retrieval or extraction) adj5 device$).tw.
18. endoluminal repair$.tw.
19. (blood vessel adj5 (prosthesis or implantat$)).tw.
20. ((merci or concentric) adj retriever).tw.

21. (endovascular snare$ or neuronet or microsnare or X-ciser or angiojet).tw.
22. or/5-21
23. 4 and 22
24. limit 23 to humans
25. Randomized Controlled Trials as Topic/
26. random allocation/
27. Controlled Clinical Trials as Topic/
28. control groups/
29. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
30. double-blind method/
31. single-blind method/
32. Therapies, Investigational/
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
36. random$.tw.
37. (controlled adj5 (trial$ or stud$)).tw.
38. (clinical$ adj5 trial$).tw.
39. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
40. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
41. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
42. (coin adj5 (flip or flipped or toss$)).tw.
43. or/25-42
44. 24 and 43

Appendix 2. Embase search strategy

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/ or stroke patient/ or stroke unit/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. 1 or 2 or 3
5. interventional radiology/ or endovascular surgery/
6. percutaneous transluminal angioplasty/ or angioplasty/ or laser angioplasty/ or catheterization/ or catheter ablation/ or balloon dilatation/ or exp atherectomy/
7. stent/
8. thrombectomy/ or exp percutaneous thrombectomy/ or embolectomy/
9. artery prosthesis/
10. cerebral revascularization/ or reperfusion/ or artery dilatation/ or recanalization/
11. (interventional adj3 (radiolog$ or radiograph$ or neuroradiolog$)).tw.
12. (angioplast$ or stent$).tw.
13. (thrombectomy or embolectomy or atherect$).tw.
14. thromboaspiration.tw.
15. ((mechanical or radiolog$ or pharmacomechanical or laser or endovascular or neurovascular) adj5 (thrombolys$ or reperfusion or fragmentation or aspiration or recanali?ation or clot lys$)).tw.
16. ((clot or thrombus or thrombi or embol$) adj5 (aspirat$ or remov$ or retriev$ or fragmentation or retract$ or extract$ or obliterat$ or dispers$)).tw.
17. ((retrieval or extraction) adj5 device$).tw.
18. endoluminal repair$.tw.
19. ((blood vessel or artery) adj5 (prosthesis or implantat$)).tw.
20. ((merci or concentric) adj retriever).tw.
21. (endovascular snare$ or neuronet or microsnare or X-ciser or angiojet).tw.
22. ultrasound/ or exp ultrasound therapy/ or echography/ or doppler echography/ or intravascular ultrasound/
23. (ultrasound$ or ultrasonic$ or ultrasonogra$ or sonograph$ or insonation).tw.
24. ((transcranial adj5 doppler) or TCD or TCCD).tw.
25. fibrinolytic therapy/
26. fibrinolytic agent/ or plasmin/ or plasminogen/ or exp plasminogen activator/
27. blood clot lysis/
28. fibrinolysis/

29. (thromboly$ or fibrinoly$ or recanalis$ or recanaliz$ or sonolys$).tw.
30. ((clot$ or thrombus) adj5 (lyse or lysis or dissolve$ or dissolution or fragment$)).tw.
31. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
32. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase).tw.
33. (sonothrombolysis or sonothromboly$ or sonothrombotripsy or thrombotripsy).tw.
34. or/22-33
35. intraarterial drug administration/
36. (intra arterial or intra-arterial or intraarterial or IA).tw.
37. 35 or 36
38. 34 and 37
39. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 38
40. 4 and 39
41. Randomized Controlled Trial/
42. Randomization/
43. Controlled Study/
44. control group/
45. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/
46. Double Blind Procedure/
47. Single Blind Procedure/ or triple blind procedure/
48. random$.tw.
49. (controlled adj5 (trial$ or stud$)).tw.
50. (clinical$ adj5 trial$).tw.
51. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
52. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
53. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
54. (coin adj5 (flip or flipped or toss$)).tw.
55. or/41-54
56. 40 and 55
57. limit 56 to human
58. (carotid or hemorrhag$ or haemorrhag$ or aneurysm$ or fibrillation or trauma$ or aort$ or coronary or myocardial).ti.
59. 57 not 58

Appendix 3. CENTRAL search strategy

IDSearchHits
#1MeSH descriptor: [Cerebrovascular Disorders] this term only1430
#2MeSH descriptor: [Basal Ganglia Diseases] this term only283
#3MeSH descriptor: [Brain Ischemia] explode all trees3575
#4MeSH descriptor: [Carotid Artery Diseases] this term only472
#5MeSH descriptor: [Carotid Artery Thrombosis] this term only18
#6MeSH descriptor: [Carotid Artery Thrombosis] this term only18
#7MeSH descriptor: [Intracranial Arterial Diseases] this term only10
#8MeSH descriptor: [Cerebral Arterial Diseases] this term only26
#9MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees310
#10MeSH descriptor: [Stroke] explode all trees9629
#11(isch?emi* near/6 (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or cva)):ti,ab,kw14611
#12((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebr* or mca* or anterior circulation) near/5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab,kw16567
#13{or #1-#12}30947
#14MeSH descriptor: [Radiography, Interventional] this term only295
#15MeSH descriptor: [Radiology, Interventional] this term only36
#16MeSH descriptor: [Catheterization] this term only1615
#17MeSH descriptor: [Angioplasty] this term only293
#18MeSH descriptor: [Angioplasty, Balloon] this term only590
#19MeSH descriptor: [Angioplasty, Balloon, Laser-Assisted] this term only26
#20MeSH descriptor: [Angioplasty, Laser] this term only25
#21MeSH descriptor: [Atherectomy] this term only24
#22MeSH descriptor: [Catheter Ablation] this term only1416
#23MeSH descriptor: [Stents] explode all trees4145
#24MeSH descriptor: [Thrombectomy] this term only265
#25MeSH descriptor: [Thrombectomy] this term only265

#26MeSH descriptor: [Blood Vessel Prosthesis] this term only435
#27MeSH descriptor: [Blood Vessel Prosthesis Implantation] this term only447
#28MeSH descriptor: [Cerebral Revascularization] this term only56
#29MeSH descriptor: [Reperfusion] this term only101
#30MeSH descriptor: [Dilatation] this term only425
#31(interventional near/3 (radiolog* or radiograph* or neuroradiolog*)):ti,ab,kw861
#32(angioplast* or stent*):ti,ab,kw20793
#33(thrombectomy or thromboaspiration or embolectomy or atherect*):ti,ab,kw1961
#34(sonothrombolysis):ti,ab,kw101
#35((mechanical or radiolog* or pharmacomechanical or laser or endovascular or neurovascular) near/5 (thrombolys* or reperfusion or fragmentation or aspiration or recanali?ation or clot lys*)):ti,ab,kw783
#36((clot or thrombus or thrombi or embol*) near/5 (aspirat* or remov* or retriev* or fragmentation or retract* or extract* or obliterat* or dispers*)):ti,ab,kw808
#37((retrieval or extraction) near/5 device*):ti,ab,kw131
#38(endoluminal repair*):ti,ab,kw22
#39(blood vessel near/5 (prosthesis or implantat*)):ti,ab,kw833
#40((merci or concentric) near/5 retriever):ti,ab,kw25
#41(endovascular snare* or neuronet or microsnare or X-ciser or angiojet):ti,ab,kw32
#42{or #14-#41}27215
#43#13 and #42 with Cochrane Library publication date Between Sep 2016 and Sep 2020, in Trials1763

Appendix 4. Web of Science search strategy

#1TS=(isch?emi* NEAR/6 (stroke* or apoplex* or “cerebral vasc*” or cerebrovasc* or cva))
#2TS=((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or “middle cerebr*” or mca* or “anterior circulation”) NEAR/5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*))
#3#1 or #2
#4TS=(interventional NEAR/3 (radiolog* or radiograph* or neuroradiolog*))
#5TS=(angioplast* or stent*)
#6TS=(thrombectomy or thromboaspiration or embolectomy or atherect*)
#7TS=sonothrombolysis
#8TS=((mechanical or radiolog* or pharmacomechanical or laser or endovascular or neurovascular) NEAR/5 (thrombolys* or reperfusion or fragmentation or aspiration or recanali?ation or clot lys*))
#9TS= ((clot or thrombus or thrombi or embol*) NEAR/5 (aspirat* or remov* or retriev* or fragmentation or retract* or extract* or obliterat* or dispers*))
#10TS=((retrieval or extraction) NEAR/5 device*)
#11TS=”endoluminal repair*”
#12TS=(blood vessel NEAR/5 (prosthesis or implantat*))
#13TS=((merci or concentric) NEAR/5 retriever)
#14TS=(“endovascular snare*” or neuronet or microsnare or X-ciser or angiojet)
#15#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16#3 and #15

Appendix 5. ClinicalTrials.gov search strategy

US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
(thrombectomy OR thromboaspiration OR embolectomy OR endovascular) AND AREA[StudyType] EXPAND[Term] COVER[FullMatch] "Interventional" AND AREA[ConditionSearch] (ischaemic stroke OR brain infarction OR brain ischemia OR carotid artery obstruction OR cerebral ischemia) AND AREA[StudyFirstPostDate] EXPAND[Term] RANGE[09/20/2016, 09/01/2020]
World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch)
Basic search:
1. thrombectomy AND stroke OR thrombectomy AND stroke OR thromboaspiration AND stroke OR embolectomy AND stroke OR endovascular AND stroke
Phases are: ALL
2. thrombectomy AND brain infarction OR thrombectomy AND brain infarction OR thromboaspiration AND brain infarction OR embolectomy AND brain infarction OR endovascular AND brain infarction
Phases are: ALL
3. thrombectomy AND cerebral OR thrombectomy AND cerebral OR thromboaspiration AND cerebral OR embolectomy AND cerebral OR endovascular AND cerebral
Phases are: ALL

WHAT'S NEW

Date	Event	Description
9 August 2021	Amended	Amendments made throughout the review.

HISTORY

Protocol first published: Issue 1, 2009
Review first published: Issue 10, 2010

Date	Event	Description
25 June 2021	Amended	Acknowledgements section amended
15 June 2021	Amended	Title of plain language summary changed
2 December 2020	New citation required and conclusions have changed	The conclusion has changed from the earlier published version, as there is no longer a need for further trials to confirm these results, as was stated in previously published version. The title of the review has changed from 'Percutaneous vascular interventions for acute ischaemic stroke' to 'Endovascular thrombectomy for acute ischaemic stroke'.
1 September 2020	New search has been performed	Review is updated to 1 September 2020 and includes 15 new trials and 3443 new participants. The review now has 19 trials with 3793 participants.

CONTRIBUTIONS OF AUTHORS

All authors drafted the manuscript and approved its content. Eivind Berge passed away in February 2020. Eivind Berge made a substantial contribution to this review before his passing, contributing to the protocol, the design of data extraction sheets, and data extraction. Most of the statistical analysis was done after his passing. All remaining authors deem it highly appropriate and approve that Eivind Berge is listed as author.

DECLARATIONS OF INTEREST

Melinda B Roaldsen:

- Grants and contracts: National Institute for Health Research (NIHR) Cochrane Review Incentive Scheme to be paid on publication of this update. The award will be received by my institution.
- Work as a health professional: "I am a MD and hold a position as a Resident at the Neurological Department in Tromsø, Norway. Currently on leave from clinical work to do research."
- Institution: University Hospital of North Norway, Tromsø, Norway

Mirza Jusufovic: none known
Eivind Berge: none known (deceased)
Haakon Lindekleiv: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Other, Norway

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The name of this review has changed from: 'Percutaneous vascular interventions for acute ischaemic stroke' to: 'Endovascular thrombectomy for acute ischaemic stroke', as that latter is the more common and widespread definition and nomenclature used in both clinical practice and the scientific literature. This change has no implications for the original scope of the review, and is simply a change in terminology.

The previous version of the review included searching of Science Citation Index, ISI Proceedings, LILACS (Latin American and Caribbean Health Sciences Literature database), Google Scholar, ACP Journal Club, DARE (Database of Abstracts of Reviews of Effects), ProQuest Dissertations & Theses, British Library Theses Service, and the National Research Register Archive, as well as handsearching selected journals (*American Journal of Neuroradiology*, *Brain*, *Neuroradiology*, and *Stroke*) (O'Rourke 2010). Based on our experience from the first version of the review, we omitted searches in these sources, as they did not yield additional results and involved considerable efforts.

The previous version of this review included impairment at end of follow-up (e.g. Barthel Index score) as a secondary outcome measure. We did not include this in the updated version because all studies reported functional outcome according to the modified Rankin Scale, and none reported Barthel Index score. Impairment is also covered by the modified Rankin Scale.

In the protocol, we planned to extract time to actual delivery of endovascular thrombectomy therapy. This proved to be very difficult, as most trials reported time to groin puncture or initiation of intra-arterial treatment, therefore we employed the latter in the review.

The subgroup and sensitivity analyses methodology was updated to reflect that these could be performed on specific outcomes. We also included additional subgroups, as the newly included studies identified important subgroups that were not described in our protocol. This is further described in the Methods.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Cause of Death; Fibrinolytic Agents [*administration & dosage]; Infarction, Middle Cerebral Artery [therapy]; Intracranial Hemorrhages [epidemiology] [etiology]; Ischemic Stroke [drug therapy] [*therapy]; Mechanical Thrombolysis [*methods]; Randomized Controlled Trials as Topic; Thrombolytic Therapy [*methods]; Urokinase-Type Plasminogen Activator [administration & dosage]

MeSH check words

Aged; Female; Humans; Male; Middle Aged