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Percutaneous vascular interventions versus intravenous thrombolytic treatment for acute ischaemic stroke (Review)

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[Intervention Review]

Percutaneous vascular interventions versus intravenous thrombolytic treatment for acute ischaemic stroke

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ABSTRACT

Background

Most ischaemic strokes are caused by blockage of a cerebral artery by a thrombus. Intravenous administration of recombinant tissue plasminogen activator given within 4.5 hours is now standard treatment for this condition. Percutaneous vascular interventions use an intra-arterial, mechanical approach for thrombus disruption or removal (thrombectomy). Recent randomised trials indicate that percutaneous vascular interventions are superior to usual care (usual care usually included intravenous thrombolysis). However, intravenous thrombolysis was usually given in both arms of the trial and there was a lack of direct comparison of percutaneous vascular interventions with intravenous thrombolysis.

Objectives

To assess the effectiveness and safety of percutaneous vascular interventions compared with intravenous thrombolytic treatment for acute ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (last search: August 2018). In addition, in September 2017, we searched the following electronic databases: CENTRAL, MEDLINE, Embase, and Science Citation Index; and Stroke Trials Registry, and US National Institutes of Health Ongoing Trials Register, ClinicalTrials.gov.

Selection criteria

Randomised controlled trials (RCTs) that directly compared a percutaneous vascular intervention with intravenous thrombolytic treatment in people with acute ischaemic stroke.

Data collection and analysis

Two review authors applied the inclusion criteria, extracted data, and assessed risk of bias. We obtained both published and unpublished data. We assessed the quality of the evidence using the GRADE approach.

Main results

We included four trials with 450 participants. Data on functional outcome and death at end of follow-up were available for 443 participants from three trials. Compared with intravenous thrombolytic therapy, percutaneous vascular intervention did not improve the proportion of participants with good functional outcome (modified Rankin Scale score 0 to 2, risk ratio (RR) 1.01, 95% confidence interval (CI) 0.82 to 1.25, $P = 0.92$). The quality of evidence was low (outcome assessment was blinded, but not the treating physician or participants). At the

end of follow-up, there was a non-significant increase in the proportion of participants who died in the percutaneous vascular intervention group (RR 1.34, 95% CI 0.84 to 2.14, $P = 0.21$). The quality of evidence was low (wide confidence interval). There was no difference in the proportion of participants with symptomatic intracranial haemorrhages between the intervention and control groups (RR 0.99, 95% CI 0.50 to 1.95, $P = 0.97$). The quality of evidence was low (wide confidence interval). Data on vascular status (recanalisation rate) were only available for seven participants from one trial; we considered this inadequate for statistical analyses.

Authors' conclusions

The present review directly compared intravenous thrombolytic treatment with percutaneous vascular interventions for ischaemic stroke. We found no evidence from RCTs that percutaneous vascular interventions are superior to intravenous thrombolytic treatment with respect to functional outcome. Quality of evidence was low (outcome assessment was blinded, but not the treating physician or participants). New trials with adequate sample sizes are warranted because of the rapid development of new techniques and devices for such interventions.

PLAIN LANGUAGE SUMMARY

Treatments through the artery versus clot-dissolving drugs for the early treatment of stroke

Review question

Are there differences in the safety and effectiveness of treatments delivered into the blocked artery (percutaneous vascular interventions) and clot-dissolving drugs (intravenous thrombolysis) in the early treatment of stroke.

Background

Most strokes are caused by a blockage of an artery in the brain by a blood clot. Prompt treatment with clot-dissolving drugs (thrombolysis) can restore blood flow and prevent brain damage. The development of treatments delivered through a tube into the artery (percutaneous vascular interventions) has led to new possibilities in the treatment of stroke. This approach gives direct access to the blood clot, which can be mechanically removed or dissolved. Despite widespread use of these treatments it is unclear whether they are more effective and safe than clot-dissolving drugs given by injection (intravenous thrombolysis).

Study characteristics

We included four trials with 450 participants randomised to either percutaneous vascular intervention or clot-dissolving drugs given by injection.

Search date

The evidence is current as of September 2017.

Key results

Compared with clot-dissolving drugs, percutaneous vascular interventions did not increase the chance of making a good recovery by the end of the trial. There was no significant increase in the risk of dying or of suffering a brain bleed. New, larger trials are needed, particularly because of the rapid development of new techniques and devices for percutaneous vascular interventions.

Quality of the evidence

We judged the quality of the evidence to be low because of the limited amount of trial information available.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Percutaneous vascular interventions compared to intravenous thrombolytic treatment for acute ischaemic stroke

Percutaneous vascular interventions compared to intravenous thrombolytic treatment for acute ischaemic stroke

Patient: people with acute ischaemic stroke

Setting: hospital

Intervention: percutaneous vascular interventions

Comparison: intravenous thrombolytic treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with intravenous thrombolytic treatment	Risk with percutaneous vascular interventions				
Good functional outcome (mRS score 0-2) Follow-up: 90 days	Study population		RR 1.01 (0.82 to 1.25)	443 (3 RCTs)	⊕⊕⊕⊖ Low	Devices used for percutaneous vascular intervention differed between studies and predate modern devices. Outcome assessment was blinded, but not treating physician or participants
	433 per 1000	437 per 1000 (355 to 541)				
Death Follow-up: 90 days	Study population		RR 1.34 (0.84 to 2.14)	443 (3 RCTs)	⊕⊕⊕⊖ Low	Devices used for percutaneous vascular intervention differed between studies and predate modern devices
	160 per 1000	214 per 1000 (134 to 342)				
Symptomatic intracranial haemorrhage within first 14 days	Study population		RR 0.99 (0.50 to 1.95)	450 (4 RCTs)	⊕⊕⊕⊖ Low	Devices used for percutaneous vascular intervention differed between studies and predate modern devices
	66 per 1000	63 per 1000				
Vascular status (recanalisation rate)	Study population		N/A	N/A	N/A	Data only available for 7 participants. We considered the sample size inadequate for statistical analyses.
	N/A	N/A				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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, 'good outcome' equals scores 0 to 2 (i.e. functional independence) and 'poor outcome' equals scores 3 to 6 (i.e. functional dependency or death); **N/A:** not applicable; **RR:** risk ratio

GRADE Working Group grades of evidence

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

Moderate quality: 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 quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

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

BACKGROUND

Description of the condition

Ischaemic stroke is one of the major causes of death and disability worldwide (Strong 2007). Stroke represents a substantial personal and financial burden on society, which most likely will increase during the coming decades as a result of ageing populations (Rosamund 2008; Strong 2007).

Most ischaemic strokes are caused by the blockage of a cerebral artery by a thrombus. Thrombolytic treatment with pharmacological agents aims to dissolve the thrombus in the cerebral artery, leading to recanalisation and restoration of blood flow and improved functional outcome.

Prompt intravenous administration of recombinant tissue plasminogen activator (rt-PA) has been the standard treatment for selected patients with acute ischaemic stroke and is currently the treatment of choice within 4.5 hours of stroke onset (Adams 2007; Del Zoppo 2009; Emberson 2014; ESO 2009; Wardlaw 2009).

Thrombolytic agents can also be administered directly at the site of the occluded cerebral artery, and the rapidly developing field of mechanical clot disruption offers alternative approaches to achieve reperfusion in acute ischaemic stroke. Recent randomised trials indicate that percutaneous vascular interventions are superior to usual care (usual care usually included intravenous thrombolysis; EXTEND-IA 2015; DAWN 2018; DEFUSE 3 2018; MR CLEAN 2015; REVASCAT 2015; SWIFT PRIME 2015). However, intravenous thrombolysis was usually given in both arms of the trial and so there is a lack of direct comparison of percutaneous vascular interventions with intravenous thrombolysis.

Description of the intervention

Percutaneous vascular interventions are intra-arterial stroke therapies that use a mechanical device for thrombus disruption or removal. The intervention may consist of manipulation of the microcatheter tip/guidewire inside the thrombus, or it may include use of devices that can be divided into five different categories.

- Thrombectomy devices are devices that retrieve a thrombus.
- Thrombus disruption devices use a guide-wire or snare to mechanically fragment a thrombus.
- Thromboaspiration devices use a microcatheter or guiding catheter to aspirate the thrombus.
- Stent devices are expandable scaffolds that entrap the thrombus between the stent and the blood vessel wall.
- Sonothrombolysis devices use ultrasonic vibrations to dissolve the thrombus.

These techniques are often combined with intra-arterial injection of thrombolytic drugs.

Intravenous thrombolytic drugs are now standard treatment of acute ischaemic stroke. The thrombolytic drug alteplase (a recombinant tissue plasminogen activator: rt-PA) has been licensed for use within 4.5 hours after onset of stroke in the USA, Canada, and most European countries. Other types of intravenous thrombolytic drugs include urokinase, recombinant pro-urokinase, streptokinase, and other recombinant

tissue plasminogen activators such as alteplase, tenecteplase, reteplase, and desmoteplase.

How the intervention might work

Percutaneous vascular interventions for acute ischaemic stroke aim to recanalise the occluded artery and restore perfusion to ischaemic brain parenchyma.

Why it is important to do this review

Percutaneous vascular interventions may be used as primary or adjunctive treatment strategies in acute ischaemic stroke and could have several potential advantages over pharmacological thrombolytics. First, these interventions may lead to a lower risk of intracranial haemorrhage and could provide improved recanalisation compared with pharmacological thrombolysis and further minimise ischaemic cerebral damage (Menon 2015). Second, they could extend the time window for treatment beyond 4.5 hours, which is the time window for intravenous rt-PA treatment. Last, percutaneous interventions could be used in patients who have contraindications to pharmacological agents (e.g. abnormal haemostasis or recent surgery).

There are also several potential disadvantages of percutaneous vascular interventions, for example the technical difficulties and the extra time that elapses before treatment can start, the need for centres with proper equipment and expertise, complications related to trauma to the vasculature (e.g. dissection, perforation, or rupture), or fragmentation of the thrombus causing distal artery occlusion.

Recent randomised trials indicate that percutaneous vascular interventions are superior to usual care (usual care usually included intravenous thrombolysis; DAWN 2018; DEFUSE 3 2018; EXTEND-IA 2015; MR CLEAN 2015; REVASCAT 2015; SWIFT PRIME 2015). However, intravenous thrombolysis was usually given in both arms of the trial and there is a lack of direct comparison of percutaneous vascular interventions with intravenous thrombolysis.

A direct comparison of these two treatments might help clinicians in selecting the best treatment option for people with acute ischaemic stroke. We therefore aimed to perform a systematic review of all RCTs that directly compared percutaneous vascular interventions with intravenous thrombolytic treatment.

OBJECTIVES

To assess the effectiveness and safety of percutaneous vascular interventions compared with intravenous thrombolytic treatment for acute ischaemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), that directly compared a percutaneous vascular intervention with intravenous thrombolytic treatment in people with acute ischaemic stroke.

Types of participants

People with acute ischaemic stroke who were eligible for treatment with an intravenous thrombolytic agent or a percutaneous vascular intervention.

Types of interventions

All percutaneous arterial endovascular techniques aimed at revascularisation in acute ischaemic stroke, including the use of the following devices:

- thrombectomy (retriever devices);
- thromboaspiration;
- mechanical fragmentation of the thrombus;
- intra-arterial sonothrombolysis.

Intra-arterial thrombolytic drugs may be given in addition to any of these treatments. The direct comparison of intra-arterial and intravenous thrombolytic drugs alone is the subject of another review ([Wardlaw 2009](#)).

The control (comparison therapy) was intravenous thrombolytic treatment, irrespective of dose or type of agent.

Types of outcome measures

Primary outcomes

Functional outcome at the end of the scheduled follow-up period, categorised by the modified Rankin Scale (mRS): good outcome: scores 0 to 2 (i.e. functional independence); poor outcome: scores 3 to 6 (i.e. functional dependency or death).

Given that some trials use the term 'favourable outcome', to denote mRS scores of 0 or 1, 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 own definition of good or poor functional outcome.

Secondary outcomes

- Deaths from all causes, both:
 - * during the first two weeks, and
 - * at the end of the scheduled follow-up period.
- Symptomatic intracranial haemorrhage within the first two weeks and at the end of the follow-up period. We defined symptomatic intracranial haemorrhage according to the criteria that were used in the third European Cooperative Acute Stroke Study (ECASS III) ([Hacke 2008](#)). When symptomatic intracranial haemorrhages were not reported according to these criteria, we used the trial's definition.
- Vascular status, according to the Cerebral Infarction Perfusion Categories ([Higashida 2003](#)), and the Thrombolysis In Myocardial Infarction (TIMI) reperfusion score ([Khatri 2005](#)).

Search methods for identification of studies

See the 'Specialised register' section on the [Cochrane Stroke](#) website. We did not apply any language restrictions to our searches. We did not identify any relevant non-English-language papers when screening the abstracts and titles.

Electronic searches

We searched the Cochrane Stroke Trials Register, which was last searched by the Managing Editor in August 2018. In addition, we searched the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 9), in the Cochrane Library ([Appendix 1](#));
- MEDLINE (from 1946 to September 2017) ([Appendix 2](#));
- Embase (from 1980 to September 2017) ([Appendix 3](#));
- Science Citation Index (from 1980 to September 2017);
- The following ongoing trials registers (last search: September 2017);
 - * Stroke Trials Registry (www.strokecenter.org/trials);
 - * US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Information Specialist and adapted it for the other databases included in this review ([Appendix 1](#); [Appendix 2](#); [Appendix 3](#)).

Searching other resources

In an effort to identify further published, unpublished, ongoing and planned trials we:

- screened reference lists of relevant trials;
- contacted the manufacturers of any interventional radiological equipment included in the review;
- contacted professional societies in neuroradiology and interventional radiology;
- contacted authors and researchers active in the field;
- handsearched conference proceedings for the World Stroke Congress, International Stroke Congress, European Stroke Congress, the annual meeting of the European Society of Neuroradiology, and the annual meeting of the American Society of Neuroradiology.

Data collection and analysis

Selection of studies

One review author (HL) screened titles and abstracts of references identified by the searches. We obtained full-paper copies of those trial reports that, from the title and abstract, appeared to be eligible for inclusion. Two review authors (HL and EB) then independently assessed these for inclusion. The review authors resolved any disagreements by discussion. When we excluded a trial we kept a record of both the report and the reason for exclusion.

Data extraction and management

Two review authors (HL and EB) 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. We extracted the following data from each report:

- diagnostic criteria used for acute ischaemic stroke, including whether MRI diffusion and perfusion mismatch, CT angiography, or CT perfusion were used to identify eligible participants;
- location of the arterial occlusion;
- time interval from stroke onset to randomisation;

- time to actual delivery of therapy/revascularisation, either percutaneous vascular or intravenous thrombolytic therapy (not start of procedure);
- numbers of participants in each treatment group with outcome events;
- modality of percutaneous vascular intervention used;
- agent and dose of pharmacological thrombolytic therapy used.

One review author (HL) entered the data into Review Manager 5 (RevMan 5) software ([Review Manager 2014](#)). Another review author (EB), checked these data against the data extraction forms to correct any clerical data entry errors. When any relevant data were missing from the available publications, we contacted the principal investigators or sponsors concerned.

Assessment of risk of bias in included studies

Two of the review authors (HL and EB) independently assessed risk of bias for each included study. We appraised selection bias by assessing the random sequence generation and allocation concealment of the intervention. We appraised performance and detection bias by assessing the blinding of participants, personnel, and outcome assessors. We appraised attrition bias by checking the number of participants lost to follow-up and participants excluded from the study, and appraised any reporting or other biases in the studies. We scored these data as low risk of bias, unclear risk, or high risk of bias.

Two review authors (HL and EB) independently performed quality assessment of reports of eligible trials; they resolved any disagreements by discussion. We used the following criteria to assess the quality of reports of eligible trials according to section 8.5.3 of the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2017](#)):

- adequate sequence generation;
- allocation concealment;
- blinding: in trials of percutaneous vascular interventions it is not possible to blind the participants or those providing the interventions. In this review, we categorised trials as 'blinded' if outcome assessors were blinded to the treatment that the participant had received;
- 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, regardless of what treatment they received, and
 - * when the numbers of participants lost to follow-up and the associated reasons were reported;
- no selective reporting;
- no 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 2017](#)).

Measures of treatment effect

For dichotomous outcomes, we calculated a weighted estimate of the treatment effects across trials and reported risk ratios (RR) with 95% confidence intervals (CI). For studies that used scales for

the assessment of similar outcomes, we reported mean differences (MD).

Dealing with missing data

If the published information did not allow intention-to-treat analysis, we planned to contact the authors to get as complete follow-up data as possible on all randomised participants for the originally proposed period of follow-up. If the data for these participants remained unavailable, we planned to provide a worst-case scenario analysis for the composite outcome of 'death and severe disability'. In this sensitivity analysis, we would assume that those participants who were lost to follow-up in the treatment group had the worst outcome while those participants who were lost to follow-up in the control group had the best outcome.

However, this was not done as no participants were lost to follow-up in any of the studies.

Assessment of heterogeneity

We used Chi² statistic and I² statistic (percentage of total variation across studies due to heterogeneity) to test for heterogeneity between trial results. We also assessed heterogeneity qualitatively ([Deeks 2017](#)).

Assessment of reporting biases

We planned to use funnel plots to assess reporting bias and to assess funnel plots qualitatively. This was not done as we did not identify enough trials to assess reporting bias by funnel plots ([Sterne 2017](#)).

Data synthesis

We calculated a weighted estimate of the typical treatment effect across trials by means of a fixed-effect model. In the case of heterogeneity of treatment effects, we planned to use the random-effects model to assess the overall treatment effects.

GRADE and 'Summary of findings' table

We used GRADE to assess the quality of evidence for the outcomes ([Schünemann 2013](#)). Two review authors (HL and EB) independently assessed the quality of evidence for each outcome. We considered RCTs as high quality but downgraded evidence based on the following.

- Limitations in the design and implementation of available studies suggesting high likelihood of bias.
- Indirectness of evidence (indirect population, intervention, control, outcomes).
- Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses).
- Imprecision of results (wide confidence intervals).
- High probability of publication bias.

We used the GRADEPro Guideline Development Tool to create [Summary of findings for the main comparison](#) and to report the quality of the evidence ([GRADEpro GDT 2015](#)).

The GRADE approach specifies four levels of quality:

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

- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect but may be substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We planned to do subgroup analyses for concomitant antithrombotic therapy, stroke severity, time since stroke symptom onset (that is, symptom onset), modality of the percutaneous vascular intervention, dose and type of agent used for intravenous thrombolytic treatment, and anatomy of the arterial occlusion. However, we did not identify enough trials to do subgroup analyses.

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

Results of the search

The searches of MEDLINE and Embase identified 2687 and 6218 citations. We removed 1068 duplicates, leaving 7837 citations for review of title and abstract. The search of CENTRAL identified 790 citations. Searches of Cochrane Stroke Group Trials Register and Science Citation Index and reviewing the reference lists of included studies did not identify any additional studies. We contacted researchers active in the field, professional organisations and manufacturers of interventional radiological equipment and received replies from Joseph Broderick, Takashi Inoue, Keith Muir, Wouter Schonewille, Michael Söderman, and Phil White, British Society of Neuroradiologists, and Penumbra Inc. This did not identify additional studies.

After reviewing the titles and abstracts, we retrieved full texts for seven studies. We excluded three studies because the control group did not receive intravenous thrombolytic medication ([Del Zoppo 1998](#); [Furlan 1999](#); [Ogawa 2007](#)). We identified one ongoing study after searching Stroke Trials Registry, ClinicalTrials.gov, and Current Controlled Trials ([NCT01455935](#)). We included four studies ([Ducrocq 2005](#); [Sen 2009](#); [SYNTHESIS Expansion 2013](#); [SYNTHESIS Pilot 2010](#)).

[Figure 1](#) shows the PRISMA flow diagram of the study selection process.

Figure 1. Study flow diagram

Included studies

We identified four trials with 450 participants randomised to percutaneous vascular interventions or intravenous thrombolysis (Ducrocq 2005; Sen 2009; SYNTHESIS Pilot 2010; SYNTHESIS Expansion 2013).

Angiographic diagnostic criteria and topography of strokes included

Three trials did not select participants based on location of the arterial occlusion (Ducrocq 2005; SYNTHESIS Expansion

2013; SYNTHESIS Pilot 2010). One trial included participants with proximal occlusion strokes in either the middle cerebral (M1 or M2), terminal internal carotid, basilar, or vertebral artery using computed tomography angiography (Sen 2009). See [Characteristics of included studies](#).

In Ducrocq 2005, all 13 participants in the intervention group had an occlusion in the middle cerebral artery trunk. Angiography was not performed in the controls. Of the seven participants included in Sen 2009, six had an occlusion in the middle cerebral artery and one had an occlusion in the internal carotid artery. In SYNTHESIS Pilot

2010, 20 participants in the intervention group had an occlusion in the anterior circulation, four in the posterior circulation, and one had an undefined location of stroke. In the control group, 27 participants had an occlusion in the anterior circulation, one participant in the posterior circulation, and one had an undefined location of stroke. In [SYNTHESIS Expansion 2013](#), 160 participants had an occlusion in the anterior circulation, 18 participants in the posterior circulation, and one participant in both the anterior and posterior circulation. In the control group, 170 participants had an occlusion in the anterior circulation and 11 participants in the posterior circulation.

Age and gender of included participants

The mean age of the participants in the intervention group in [Ducrocq 2005](#) was 60 years and in the control group 58 years. The mean age of all seven participants in [Sen 2009](#) was 68 years. The mean age of participants in the intervention group in [SYNTHESIS Pilot 2010](#) was 61 years and in the control group 64 years. The mean age of participants in the intervention group in [SYNTHESIS Expansion 2013](#) was 66 years and in the control group 67 years.

Three studies specified the number of men and women in the study groups ([Ducrocq 2005](#); [SYNTHESIS Expansion 2013](#); [SYNTHESIS Pilot 2010](#)). Across these studies, 137 (63%) of 219 participants randomised to the intervention group and 135 (60%) of 224 participants randomised to the control group were men. More men than women were randomised to the intervention group in [Ducrocq 2005](#) (12 out of 13 in the intervention group versus 9 out of 14 in

the control group). There were no gender differences in [SYNTHESIS Expansion 2013](#) and [SYNTHESIS Pilot 2010](#).

Medical history

In [Ducrocq 2005](#), the study groups were balanced with respect to the proportion of participants with hypertension, diabetes, atrial fibrillation, and dyslipidaemia. In [SYNTHESIS Expansion 2013](#), the study groups were balanced with respect to use of antihypertensive, antidiabetes, and antiplatelet therapy. However, the proportion of participants with atrial fibrillation was larger in the control group than in the intervention group (16% versus 8%). There was little information about background medical history in [Sen 2009](#) and [SYNTHESIS Pilot 2010](#).

Time interval from stroke onset to randomisation and start of procedure

[Ducrocq 2005](#) included participants with initiation of treatment within six hours after stroke onset. [Sen 2009](#) included participants randomised within three hours after stroke onset. [SYNTHESIS Pilot 2010](#) included participants with initiation of treatment within three hours after stroke onset (treatment in the intervention group was allowed up to six hours after stroke onset). [SYNTHESIS Expansion 2013](#) included participants with initiation of treatment within 4.5 hours after stroke onset.

Median time from stroke onset to start of treatment in the intervention group

	Intervention group	Control group
Ducrocq 2005	5:24 hours	4:16 hours
Sen 2009	Not reported	Not reported
SYNTHESIS Pilot 2010	3:45 hours	2:45 hours
SYNTHESIS Expansion 2013	3:15 hours	2:35 hours

Only one trial had data on the time interval from stroke onset to randomisation ([SYNTHESIS Expansion 2013](#)). This was 2:28 hours for the intervention group and 2:25 hours for the control group

Drug usage, and means of drug delivery

	Ducrocq 2005	Sen 2009	SYNTHESIS Pilot 2010	SYNTHESIS Expansion 2013
Intervention group	Intra-arterial urokinase 900,000 units	Intra-arterial rt-PA, maximum 20 mg	Intra-arterial rt-PA 0.9 mg per kg (maximum 90 mg)	Intra-arterial rt-PA 0.9 mg per kg (maximum 90 mg)
Control group	Intravenous urokinase 900,000 units	Intravenous rt-PA 0.9 mg per kg (maximum 90 mg), 10% given as a bolus dose,	Intravenous rt-PA 0.9 mg per kg (maximum 90 mg), 10% given as a bolus dose,	Intravenous rt-PA 0.9 mg per kg (maximum 90 mg), 10% given as a bolus dose,

the rest given over 1 hour the rest given over 1 hour the rest given over 1 hour

Modality of percutaneous vascular intervention used in the intervention groups

	Total	Ducrocq 2005	Sen 2009	SYNTHESIS Expansion 2013	SYNTHESIS Pilot 2010
Manipulation of microcatheter tip plus intra-arterial thrombolysis	132 (59%)	13	3	109	7
Use of device ^a in addition to manipulation of microcatheter tip plus intra-arterial thrombolysis	58 (26%)	0	0	56	2
Only intra-arterial thrombolysis (no mechanical manoeuvre)	10 (5%)	0	0	0	10
No intervention ^b	22 (10%)	0	0	16	6

^aSYNTHESIS Pilot 2010: goose-neck microsnare (n = 1) and carotid stent (n = 1). SYNTHESIS Expansion 2013: Solitaire stent (n = 18), Trevo stent (n = 5), Merci thrombus retriever device (n = 5), Penumbra thromboaspiration device (n = 9), balloon alone (n = 5), and other stents or retrievers (n = 19). In this trial some participants were treated with more than one device, so the total number of devices is higher than 56.

^bIn SYNTHESIS Pilot 2010: because of no artery occlusion on angiogram (n = 6). In SYNTHESIS Expansion 2013: because of

clinical improvement (n = 6), no artery occlusion on angiogram (n = 3), dissection (n = 3), unknown bleeding diathesis (n = 1), groin haematoma (n = 1), delayed availability of interventionist (n = 1), and equipment breakdown (n = 1).

Concomitant use of antithrombotic treatment

Intervention group	
Ducrocq 2005	Unfractionated heparin: 1000 units (bolus) plus 1000 units per hour as infusion
Sen 2009	Unfractionated heparin: 120 units per hour as infusion
SYNTHESIS Expansion 2013	Unfractionated heparin: 5000 units (bolus) plus 500 units per hour as infusion
SYNTHESIS Pilot 2010	Unfractionated heparin: 2000 units (bolus) plus 500 units per hour as infusion

Assessment of outcome

Three trials reported functional outcome at end of follow-up according to the mRS score (Ducrocq 2005; SYNTHESIS Expansion 2013; SYNTHESIS Pilot 2010). Three trials reported mortality at the end of follow-up (Ducrocq 2005; SYNTHESIS Expansion 2013; SYNTHESIS Pilot 2010). One trial was a feasibility study that did not report functional outcome or death (Sen 2009). All included trials reported symptomatic intracranial haemorrhage within 14 days.

Only one trial reported recanalisation rates according to the TIC1 classification (Sen 2009). See [Characteristics of included studies](#).

Excluded studies

We excluded three studies (Del Zoppo 1998; Furlan 1999; Ogawa 2007).

Risk of bias in included studies

See [Included studies](#), [Figure 2](#) and [Figure 3](#).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ducrocq 2005	?	+	-	-	+	+	?
Sen 2009	+	+	-	+	+	+	?
SYNTHESIS Expansion 2013	+	+	?	+	+	+	?
SYNTHESIS Pilot 2010	+	+	-	+	+	+	?

Allocation

Allocation bias was low in [Sen 2009](#); [SYNTHESIS Expansion 2013](#) and [SYNTHESIS Pilot 2010](#), which used computer-generated random number generators. The risk of bias was unclear in [Ducrocq 2005](#) as they did not describe the randomisation procedure.

Blinding

All studies were at high risk of performance bias as participants and personnel were not blinded to treatment allocation.

There was low risk of detection bias in three studies where outcome assessors were blinded to treatment allocation ([Sen 2009](#);

SYNTHESIS Expansion 2013; SYNTHESIS Pilot 2010). One trial had high risk of detection bias as the outcome assessor was not blinded to treatment allocation (Ducrocq 2005).

Incomplete outcome data

We considered the completeness of outcome data to be at low risk of bias for all included trials as no participants were lost to follow-up in any of the included trials.

Selective reporting

All trials were at low risk of bias as no participants were lost to follow-up.

Other potential sources of bias

One trial had a high risk of bias as it was terminated early due to high case fatality and suffered from a lack of statistical power (Ducrocq 2005).

Effects of interventions

See: [Summary of findings for the main comparison Percutaneous vascular interventions compared to intravenous thrombolytic treatment for acute ischaemic stroke](#)

See [Summary of findings for the main comparison](#) for the main comparison.

Functional outcome at the end of follow-up

The number of participants with a mRS score 0 to 2 at the end of follow-up was available for a total of 443 participants from three trials (Ducrocq 2005; SYNTHESIS Expansion 2013; SYNTHESIS Pilot 2010). Sen 2009 was a feasibility study of only seven participants and did not provide data on outcome. There was no evidence of an effect of the intervention on the proportion of participants with mRS scores of 0 to 2 (RR 1.01, 95% CI 0.82 to 1.25, $P = 0.92$), with no significant between-study heterogeneity ($I^2 = 58\%$, $P = 0.09$; [Analysis 1.1](#)).

The number of participants in each mRS category was available for a total of 443 participants from the same trials (Ducrocq 2005; SYNTHESIS Expansion 2013; SYNTHESIS Pilot 2010).

Participants in the intervention group had a statistically significant improvement in the mean mRS score (MD -0.43, 95% CI -0.81 to -0.04, $P = 0.03$), with no significant between-study heterogeneity ($I^2 = 0\%$, $P = 0.40$; [Analysis 1.2](#)).

Quality of evidence was low (outcome assessment was blinded, but not treating physician or participants).

Death from all causes

Data on death at the end of follow-up were available for a total of 443 participants from three trials (Ducrocq 2005; SYNTHESIS Expansion 2013; SYNTHESIS Pilot 2010). At the end of follow-up, there was a non-significant increase in the proportion of participants who died in the intervention group (RR 1.34, 95% CI 0.84 to 2.14, $P = 0.21$), with no significant between-study heterogeneity ($I^2 = 0\%$, $P = 0.72$; [Analysis 1.3](#)).

Data on death within 14 days were available for a total of 416 participants from two trials (SYNTHESIS Expansion 2013; SYNTHESIS Pilot 2010). At the end of follow-up, there was a non-

significant increase in the proportion of participants who died in the intervention group (RR 1.32, 95% CI 0.69 to 2.51, $P = 0.40$), with no significant between-study heterogeneity ($I^2 = 0\%$, $P = 0.86$; [Analysis 1.4](#)).

Quality of evidence was low (wide confidence interval).

Symptomatic intracranial haemorrhage

Data on symptomatic intracranial haemorrhages within first 14 days were available for a total of 450 participants from four trials (Ducrocq 2005; Sen 2009; SYNTHESIS Expansion 2013; SYNTHESIS Pilot 2010). There was no difference in the proportion of participants with symptomatic intracranial haemorrhages between the intervention and control groups (RR 0.99, 95% CI 0.50 to 1.95, $P = 0.97$), with no significant between-study heterogeneity ($I^2 = 0\%$, $P = 0.57$; [Analysis 1.5](#)).

Quality of evidence was low (wide confidence interval).

Vascular status (recanalisation rate)

Data on vascular status (recanalisation rate) of the occluded artery were available for a total of seven participants in one trial (Sen 2009). We considered the sample size inadequate for statistical analyses.

Subgroup analyses and sensitivity analyses

There were not enough data to perform subgroup or sensitivity analyses.

DISCUSSION

Summary of main results

The present review directly compared intravenous thrombolytic treatment with percutaneous vascular interventions for ischaemic stroke. We found no difference in the proportion of participants with good functional outcome at end of follow-up and no statistically significant differences in the risk of death or intracranial haemorrhage.

Although there was no difference in the proportion of participants with good outcome (mRS score 0 to 2), we found that percutaneous vascular interventions slightly improved the mean mRS score at follow-up compared with intravenous thrombolytic treatment. This should be interpreted with caution as the finding was not very robust and a change in mean mRS score does not describe a clinically meaningful effect.

Overall completeness and applicability of evidence

Evaluating the clinical benefit of a change in the mean mRS score difference is difficult. The mRS is a non-linear scale, and a 1-point transition from 6 to 5 qualitatively differs from a 1-point transition from 1 to 0. Dichotomous analyses of the transition from independence to dependency (mRS score 0 to 2 versus 3 to 6) may be more appropriate, although this approach does not value other clinically important transitions (such as a transition from severe dependency (mRS score 5) to the ability to walk without assistance (score 3; [Saver 2007](#)). Further, this approach reduces statistical power as participants at one end of the spectrum are less likely to cross the binary threshold and contribute data to the analysis ([Berge 2002](#)).

A major limitation of the study is the limited number of included trials. This resulted in wide confidence intervals. Further, the tests of heterogeneity when based on a limited number of studies, as it is the case in this review, has a very low power and does not provide reliable results. Substantial heterogeneity is likely present despite the tests being non-significant.

Several recent thrombectomy trials have been published ([DAWN 2018](#); [DEFUSE 3 2018](#); [EXTEND-IA 2015](#); [IMS III 2013](#); [MR CLEAN 2015](#); [MR RESCUE 2013](#); [REVASCAT 2015](#); [SWIFT PRIME 2015](#)). A majority of these trials showed benefit of percutaneous vascular interventions compared with no such therapy. However, we did not include these trials in the present meta-analysis because they did not compare directly percutaneous vascular interventions and intravenous thrombolytic therapies.

Percutaneous vascular interventions are associated with improved arterial recanalisation compared with intravenous thrombolytic treatment ([Baker 2011](#); [Goyal 2015](#)). However, our review did not find that this translated into improved clinical outcome compared with intravenous thrombolytic treatment. The cause for this is unknown. One possible explanation is that it takes more time to initiate percutaneous vascular interventions compared with intravenous thrombolytic treatment.

Quality of the evidence

The quality was low, with high risk of bias due to participants and treating physicians not blinded in the trials.

Potential biases in the review process

There is always a risk of publication bias with systematic reviews; however, we tried to avoid this by using a very comprehensive search strategy and including published and unpublished studies.

Agreements and disagreements with other studies or reviews

There is a rapid development of new percutaneous vascular interventions. Only a minority of the participants from the included studies were treated with (mostly first-generation) intra-arterial devices. The new stent retrievers have been shown to improve time to recanalisation and clinical outcome compared with the first-generation devices ([Nogueira 2012](#); [Saver 2012](#)), and may improve clinical outcome compared with intravenous thrombolytic treatment.

Unfortunately, we were not able to include these more recent trials as none of them randomised participants to intravenous versus percutaneous therapy. Instead, all trials randomised participants

to intravenous versus intravenous plus percutaneous therapy or best medical care versus best medical care plus percutaneous therapy. Caution is warranted in forgoing intravenous thrombolytic treatment in people with ischaemic stroke who are eligible for both treatments, especially if this delays time to recanalisation. However, a post-hoc analysis of pooled data from two trials of a percutaneous vascular intervention (Solitaire with the intention for thrombectomy and Solitaire flow restoration thrombectomy for acute revascularisation) found similar outcomes in subgroups of participants who were given intravenous thrombolytic treatment before percutaneous vascular intervention compared with participants who were only treated with a percutaneous vascular intervention ([Coutinho 2017](#)). However, post-hoc analyses should be interpreted with caution due to the risk of spurious findings, and a trial of forgoing intravenous thrombolytic treatment in participants with ischaemic stroke that can be given both treatments is warranted.

AUTHORS' CONCLUSIONS

Implications for practice

There was no evidence from the randomised controlled trials that directly compared percutaneous vascular interventions with intravenous thrombolytic treatment that showed that percutaneous vascular interventions were superior.

Implications for research

New trials should be of sufficient size, and should employ the latest generation devices. There may not be much equipoise among the clinical research community regarding the benefit of percutaneous interventions in proximal occlusion strokes. Future trials may, therefore, focus on people with mild-to-moderate strokes and on whether it is safe to forgo intravenous thrombolytic treatment in people with ischaemic stroke who are eligible for both treatments.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ducrocq 2005

Methods	Randomised, controlled, single-centre clinical trial
Participants	<ul style="list-style-type: none"> Age: 18-79 years Neurological deficit present for 1 h and no improvement by the time of randomisation Well-defined time of onset of symptoms, compatible with an onset of treatment within 6 h Acute neurological deficit presumed to be due to cerebral ischaemia Moderate-severe deficit with a score on the SSS ≤ 50
Interventions	<p>Intervention group: thrombus disruption using microcatheter. Intra-arterial urokinase at a dose of 900,000 U</p> <p>Control group: IV urokinase at a dose of 900,000 U</p>
Outcomes	<p>Primary outcome: mRS score 0-2 at 90 days' follow-up</p> <p>Secondary outcomes: SSS score > 52 on day 90, Barthel Index score ≥ 85 on day 90, mean SSS score on days 7, 30 and 90, mean Barthel Index on day 90, and the number of participants discharged directly to home</p> <p>Safety variables: overall mortality on day 90, number of fatal and symptomatic non-fatal intracerebral haemorrhages, and other serious AEs</p>
Notes	The study was terminated early according to prespecified criteria because of high mortality rate (26%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation procedure was not described
Allocation concealment (selection bias)	Low risk	The trial was open-label
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel were not blinded to treatment allocation

Percutaneous vascular interventions versus intravenous thrombolytic treatment for acute ischaemic stroke (Review)

Ducrocq 2005 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	ITT analyses
Other bias	Unclear risk	No

Sen 2009

Methods	Randomised, controlled, single-centre clinical trial
Participants	Inclusion criteria <ul style="list-style-type: none"> Time of presentation < 3 h from symptom onset NIHSS ≥ 4 or isolated aphasia or isolated hemianopsia Age > 18 years Ability to provide written informed consent and comply with study assessments for the full duration of the study
Interventions	<p>Intervention group: mechanical thrombus disruption using microcatheter. Intra-arterial rtPA at a maximum dose of 20 mg. Concomitant heparin flush at 2 U heparin/min</p> <p>Control group: IV t-PA at a dose of 0.9 mg/kg (maximum, 90 mg), with 10% given as an initial bolus and the remaining 90% as a constant infusion over a period of 1 h</p>
Outcomes	<p>The primary objective of the study was to test 3 areas that were deemed to be of importance in designing a future multicenter randomised trial:</p> <ul style="list-style-type: none"> feasibility of randomisation, enrolment, and treatment within the given time frame specified an evaluation of safety variables and adverse events any trend of efficacy of the 2 forms of administration of rtPA, adjusting for baseline differences if necessary, which would be useful in designing a future study <p>Other outcomes: neurological improvement (reduction in NIHSS ≥ 4) at 90 days; symptomatic and asymptomatic intracranial haemorrhages at 24 h, TIMI recanalisation on MRI 24-72 h</p>
Notes	Feasibility study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based random number generator (GraphPad Statmate, San Diego, CA)
Allocation concealment (selection bias)	Low risk	Open-label

Sen 2009 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	ITT analyses
Other bias	Unclear risk	No

SYNTHESIS Expansion 2013

Methods	Randomised, controlled, multi-centre trial
Participants	<ul style="list-style-type: none"> Age 18-80 years Sudden focal neurological deficit attributable to a stroke Clearly defined time of onset, allowing the initiation of IV treatment within 4.5 h of symptom onset and intra-arterial treatment as soon as possible and within 6 h from symptom onset (having verified the availability of the interventional neuroradiologist and taking into account all possible impediments)
Interventions	<p>Intervention group: decided by interventional neuroradiologist. Either mechanical thrombus disruption using microcatheter, suction thrombectomy (Penumbra, Penumbra Inc), stenting (Solitaire, E3/Covidien; Trevo, Concentric/Stryker), clot extraction by retrieval device (Merci, Concentric/Stryker). Intra-arterial rtPA at a dose of 0.9 mg/kg (maximum: 90 mg) could be given either alone or in addition to mechanical clot disruption. Concomitant heparin flush with 5000 U bolus, followed by 500 U/h</p> <p>Control group: IV t-PA at a dose of 0.9 mg/kg (maximum: 90 mg), with 10% given as an initial bolus and the remaining 90% as a constant infusion over a period of 1 h</p>
Outcomes	<p>Primary outcome: disability-free survival at 90 days, with freedom from disability defined as a mRS score 0-1</p> <p>Secondary outcomes: proportion of participants with NIHSS score ≤ 6</p> <p>Safety measures: assessed at day 7 after thrombolysis: fatal and non-fatal symptomatic intracranial haemorrhage, fatal and non-fatal symptomatic oedema from an original brain infarction, fatal and non-fatal recurrent ischaemic stroke, death from any cause, neurologic deterioration (increase of ≥ 4 points in the NIHSS score), and fatal and non-fatal extracerebral events</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A single randomisation list was prepared with the use of a software system, available at www.random.org/

SYNTHESIS Expansion 2013 (Continued)

Allocation concealment (selection bias)	Low risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel were not blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	ITT analyses
Other bias	Unclear risk	No

SYNTHESIS Pilot 2010

Methods	Randomised, controlled, multi-centre trial
Participants	<ul style="list-style-type: none"> Age 18-80 years Sudden focal neurological deficit attributable to a stroke Clearly defined time of onset, allowing initiation of IV treatment within 3 h of symptom onset and intra-arterial treatment as soon as possible and, in any case, within 6 h from symptom onset (having verified the availability of the interventional neuroradiologist and taking into account all possible impediments)
Interventions	<p>Intervention group: decided by interventional neuroradiologist. Either mechanical thrombus disruption using microcatheter, suction thrombectomy, clot extraction by retrieval device. Intra-arterial rtPA at a dose of 0.9 mg/kg (maximum: 90 mg) could be given either alone or in addition to mechanical clot disruption. Concomitant heparin flush with 2000 U bolus, followed by 500 U per hour</p> <p>Control group: IV t-PA at a dose of 0.9 mg/kg (maximum: 90 mg), with 10% given as an initial bolus and the remaining 90% as a constant infusion over a period of 1 h</p>
Outcomes	<p>Primary outcomes: mRS score 0-2 at 90 days' follow-up</p> <p>Secondary outcomes: decrease in NIHSS, baseline to day 7; neurological deterioration (≥ 4-point NIHSS) on day 7; any neurological deterioration during the first 7 days; all-cause death</p>
Notes	Pilot study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment to treatment was stratified per centre and prepared in a ratio 1:1 with casual numbers by a person not involved in the recruitment and not operating in any of the recruiting centres. This person prepared opaque, sealed envelopes that were sequentially opened by the randomising investigators

SYNTHESIS Pilot 2010 (Continued)

Allocation concealment (selection bias)	Low risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	ITT analyses
Other bias	Unclear risk	No

AE: adverse event; **ITT:** intention-to-treat; **IV:** intravenous; **MRI:** magnetic resonance imaging; **mRS:** modified Rankin Scale; **NIHSS:** National Institutes of Health Stroke Scale; **rtPA:** recombinant tissue plasminogen activator; **SSS:** Scandinavian Stroke Scale; **t-PA:** tissue plasminogen activator; **TIMI:** Thrombolysis In Myocardial Infarction; **U:** units

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Del Zoppo 1998	Control group did not receive IV thrombolytic medication
Furlan 1999	Control group did not receive IV thrombolytic medication
Ogawa 2007	Control group did not receive IV thrombolytic medication

IV: intravenous

Characteristics of ongoing studies [ordered by study ID]

NCT01455935

Trial name or title	Wake up Symptomatic Stroke - Benefit of Intravenous Clot Busters or Endovascular Intervention "WASSABI"
Methods	Phase 2, randomised trial
Participants	<ul style="list-style-type: none"> Age 18-80 years Ischaemic stroke presenting on awakening NIHSS score 8-22 Perfusion-diffusion mismatch on CT perfusion Alberta Stroke Program Early CT Score ≥ 7
Interventions	3 groups: <ul style="list-style-type: none"> endovascular stroke therapy (including devices and intra-arterial rtPA)

Percutaneous vascular interventions versus intravenous thrombolytic treatment for acute ischaemic stroke (Review)

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NCT01455935 (Continued)

- IV rtPA
- best medical therapy (no thrombolysis or percutaneous vascular interventions)

Outcomes	Primary outcome: mRS score 0-2 at 90 days' follow-up
Starting date	November 2011
Contact information	Tareq Kass-Hout, MD, Jacobs Neurological Institute, University of Buffalo, Buffalo, New York, USA. E-mail: kasshouttareq@gmail.com
Notes	Number of participants to be enrolled: 90 Estimated study completion: unknown; study protocol required changes after recent trials of endovascular treatment for acute ischaemic stroke (Tareq Kass-Hout, personal communication, September 2017) Clinicaltrials.gov identifier: NCT01455935

CT: computed tomography; **IV:** intravenous; **mRS:** modified Rankin Scale; **NIHSS:** National Institutes of Health Stroke Scale; **rtPA:** recombinant tissue plasminogen activator

DATA AND ANALYSES

Comparison 1. Percutaneous vascular interventions versus intravenous thrombolytic treatment for acute ischaemic stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Modified Rankin scale score 0-2	3	443	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.82, 1.25]
2 Modified Rankin scale score, continuous	3	443	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.81, -0.04]
3 All-cause death at the end of follow-up	3	443	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.84, 2.14]
4 All-cause death within 14 days	2	416	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.69, 2.51]
5 Symptomatic intracranial haemorrhages within first 14 days	4	450	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.50, 1.95]

Analysis 1.1. Comparison 1 Percutaneous vascular interventions versus intravenous thrombolytic treatment for acute ischaemic stroke, Outcome 1 Modified Rankin scale score 0-2.

Study or subgroup	Percutaneous vascular... n/N	Iv thrombolytic treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ducrocq 2005	6/13	4/14		4%	1.62[0.59,4.46]

Analysis 1.2. Comparison 1 Percutaneous vascular interventions versus intravenous thrombolytic treatment for acute ischaemic stroke, Outcome 2 Modified Rankin scale score, continuous.

Analysis 1.3. Comparison 1 Percutaneous vascular interventions versus intravenous thrombolytic treatment for acute ischaemic stroke, Outcome 3 All-cause death at the end of follow-up.

Analysis 1.4. Comparison 1 Percutaneous vascular interventions versus intravenous thrombolytic treatment for acute ischaemic stroke, Outcome 4 All-cause death within 14 days.

Analysis 1.5. Comparison 1 Percutaneous vascular interventions versus intravenous thrombolytic treatment for acute ischaemic stroke, Outcome 5 Symptomatic intracranial haemorrhages within first 14 days.

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL)

- [mh ^"cerebrovascular disorders"] or [mh ^"basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh ^"carotid artery diseases"] or [mh ^"carotid artery thrombosis"] or [mh ^"intracranial arterial diseases"] or [mh ^"cerebral arterial diseases"] or [mh "intracranial embolism and thrombosis"] or [mh stroke]
- isch*emi* near/6 (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva)
- (brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or mca* or "anterior circulation") near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)
- #1 or #2 or #3
- [mh ^"radiography, interventional"] or [mh ^"radiology, interventional"]
- [mh ^catheterization] or [mh ^angioplasty] or [mh ^"angioplasty, balloon"] or [mh ^"angioplasty, balloon, laser-assisted"] or [mh ^"angioplasty, laser"] or [mh ^atherectomy] or [mh ^"balloon dilatation"] or [mh ^catheter ablation]
- [mh ^Stents]
- [mh ^thrombectomy] or [mh ^embolectomy]
- [mh ^"blood vessel prosthesis"] or [mh ^"blood vessel prosthesis implantation"]
- [mh ^"Cerebral Revascularization"] or [mh ^reperfusion] or [mh ^dilatation]
- interventional near/3 (radiolog* or radiograph* or neuroradiolog*)
- angioplast* or stent*
- thrombectomy or embolectomy or atherect*

14. thromboaspiration or arterial next recanalization
15. (mechanical or radiolog* or pharmacomechanical or laser or endovascular or neurovascular) near/5 (thrombolys* or reperfusion or fragment* or aspiration or recanalization or clot next lys*)
16. (clot or thrombus or thrombi or embol*) near/5 (aspirat* or remov* or retriev* or fragment* or retract* or extract* or obliterated* or dispers*)
17. (retrieval or extraction) near/5 device*
18. "endoluminal repair"
19. blood vessel near/5 (prosthesis or implantat*)
20. (merci or concentric) next retriever
21. endovascular next snare* or neuronet or microsnare or "X-ciser" or angiojet
22. [mh ^ultrasonics] or [mh ^"ultrasonic therapy"] or [mh ^ultrasonography] or [mh "ultrasonography, Doppler"] or [mh ^"ultrasonography, interventional"]
23. ultrasound* or ultrasonic* or ultrasonogra* or sonograph* or insonation
24. (transcranial near/5 doppler) or TCD or TCCD
25. [mh/US].
26. sonothrombolysis or sonothromboly* or sonolys* or sonothrombotripsy or thrombotripsy
27. {OR #5-#26}
28. [mh ^"thrombolytic therapy"]
29. [mh ^"fibrinolytic agents"] or [mh ^plasmin] or [mh ^plasminogen] or [mh ^"tissue plasminogen activator"] or [mh "plasminogen activators"] or [mh ^"urokinase-type plasminogen activator"]
30. [mh ^fibrinolysis]
31. thromboly* or fibrinoly* or recanaliz* or recanaliz*
32. (clot* or thrombus) near/5 (lyse or lysis or dissolve* or dissolution)
33. tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse
34. 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
35. #28 or #29 or #30 or #31 or #32 or #33 or #34
36. #4 and #27 and #35

Appendix 2. MEDLINE (Ovid) search strategy

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 embolectomy/ or catheter ablation/
7. stents/
8. thrombectomy/ or embolectomy/ or mechanical thrombolysis/
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 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 recanalization 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 obliterated\$ 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. ultrasonics/ or ultrasonic therapy/ or ultrasonography/ or exp ultrasonography, doppler/ or ultrasonography, interventional/
23. (ultrasound\$ or ultrasonic\$ or ultrasonogra\$ or sonograph\$ or insonation).tw.
24. ((transcranial adj5 doppler) or TCD or TCCD).tw.
25. ultrasonography.fs.
26. thrombolytic therapy/

27. fibrinolytic agents/ or plasmin/ or plasminogen/ or tissue plasminogen activator/ or exp plasminogen activators/ or urokinase-type plasminogen activator/
28. fibrinolysis/
29. (thromboly\$ or fibrinoly\$ or recanaliz\$ 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. infusions, intra-arterial/
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 Trials as Topic/
42. random allocation/
43. Controlled Clinical Trials as Topic/
44. control groups/
45. 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/
46. double-blind method/
47. single-blind method/
48. therapies, investigational/
49. randomized controlled trial.pt.
50. controlled clinical trial.pt.
51. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
52. (random\$ or RCT or RCTs).tw.
53. (controlled adj5 (trial\$ or stud\$)).tw.
54. (clinical\$ adj5 trial\$).tw.
55. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
56. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
57. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
58. trial.ti
59. or/41-58
60. 40 and 59
61. exp animals/ not humans.sh
62. (carotid or hemorrhag\$ or haemorrhag\$ or aneurysm\$ or fibrillation or trauma\$ or aort\$ or coronary or myocardial).ti.
63. 60 not (61 or 62)

Appendix 3. Embase (Ovid) 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 or attack\$)).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 or arterial recanali?ation).tw.

15. ((mechanical or radiolog\$ or pharmacomechanical or laser or endovascular or neurovascular) adj5 (thrombolys\$ or reperfusion or fragment\$ or aspiration or recanaliz\$ or clot lysis\$)).tw.
16. ((clot or thrombus or thrombi or embol\$) adj5 (aspirat\$ or remov\$ or retriev\$ or fragment\$ or retract\$ or extract\$ or obliterate\$ 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. (sonothrombolysis or sonothromboly\$ or sonolys\$ or sonothrombotripsy or thrombotripsy).tw.
26. or/5-25
27. fibrinolytic therapy/
28. fibrinolytic agent/ or plasmin/ or plasminogen/ or exp plasminogen activator/
29. blood clot lysis/
30. fibrinolysis/
31. (thromboly\$ or fibrinoly\$ or recanaliz\$ or recanaliz\$).tw.
32. ((clot\$ or thrombus) adj5 (lyse or lysis or dissolve\$ or dissolution)).tw.
33. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
34. (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.
35. or/27-34
36. Randomized Controlled Trial/
37. Randomization/
38. Controlled Study/
39. control group/
40. 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/
41. Double Blind Procedure/
42. Single Blind Procedure/ or triple blind procedure/
43. random\$.tw.
44. (controlled adj5 (trial\$ or stud\$)).tw.
45. (clinical\$ adj5 trial\$).tw.
46. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
47. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
48. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
49. (coin adj5 (flip or flipped or toss\$)).tw.
50. (latin square or versus or controls).tw.
51. or/36-50
52. 4 and 26 and 35 and 51
53. limit 52 to human

Appendix 4. Other databases

"Intra arterial" or "Percutaneous vascular interventions" or "endovascular" or "thrombectomy"

AND

"intravenous"

AND

"stroke"

WHAT'S NEW

Date	Event	Description
6 November 2018	Amended	Minor corrections to search methods

CONTRIBUTIONS OF AUTHORS

HL: guarantor for the review, acquisition of data, analyses, drafting of the review

EB: acquisition of data, analyses, design of the review, drafting of protocol and review

KBS and JW: drafting of protocol, commenting on protocol and review drafts

All co-authors revised the review for intellectual content.

DECLARATIONS OF INTEREST

Haakon Lindekleiv: none known

Eivind Berge: none known

Karsten Bruins Slot: KBS is currently employed by F. Hoffmann-La Roche (Roche Norge AS). The data included in this review are based on research which has had no influence or involvement by F. Hoffmann-La Roche by any means. The views expressed in this review are the personal views of KBS and should not be understood or quoted as being made on behalf of or reflecting the position of F. Hoffmann-La Roche.

Joanna M Wardlaw: none known

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Internal sources

- No sources of support supplied

External sources

- South-Eastern Norway Regional Health Authority, Norway.

Educational grant

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol defined that we should include "participants with a definite ischaemic stroke confirmed by either a computerised tomography (CT) or magnetic resonance imaging (MRI) scan, who are eligible for treatment with an intravenous thrombolytic agent or a percutaneous vascular intervention, or both". We included participants with acute ischaemic stroke based on the individual trials' definition of ischaemic stroke.

We did not search Google Scholar because it did not understand the expert search strings and was unable to translate them. We did not search Cochrane Peripheral Vascular Diseases' Trials Register, as we considered Cochrane Stroke's Trials Register adequate for identifying possible trials.

During the work on this review, Current Controlled Trials (www.controlled-trials.com), changed its name to ISRCTN. However, the website states that the ISRCTN trial search is under review and not available. We searched Current Controlled Trials up to September 2016. Searching Current Controlled Trials did not yield references not found in other databases. As ISRCTN was not available, we excluded it as a database in our review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Thrombectomy [instrumentation] [methods]; Carotid Artery Thrombosis [drug therapy] [surgery]; Infarction, Middle Cerebral Artery [drug therapy] [surgery]; Intracranial Hemorrhages [epidemiology]; Outcome Assessment, Health Care; Randomized Controlled Trials as Topic; Stroke [*drug therapy] [etiology] [mortality] [*surgery]; Thrombolytic Therapy [*methods]

MeSH check words

Aged; Female; Humans; Male; Middle Aged