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## **Percutaneous vascular interventions for acute ischaemic stroke.**

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# Percutaneous vascular interventions for acute ischaemic stroke (Review)

O'Rourke K, Berge E, Walsh CD, Kelly PJ



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[Intervention Review]

# Percutaneous vascular interventions for acute ischaemic stroke

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## ABSTRACT

### Background

Most disabling strokes are due to 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 percutaneous vascular interventions can cause bleeding in the brain.

### Objectives

To assess the safety and efficacy of percutaneous vascular interventions in patients with acute ischaemic stroke.

### Search methods

We searched the Trials Registers of the Cochrane Stroke Group and Cochrane Peripheral Vascular Diseases Group (last searched May 2010), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 5), MEDLINE (1980 to May 2010), EMBASE (1980 to May 2010) and eight additional databases. We also searched trials registers, screened reference lists, contacted researchers and equipment manufacturers, and handsearched journals and conference proceedings.

### Selection criteria

Randomised, controlled and unconfounded trials of any percutaneous vascular intervention compared with control in patients with definite ischaemic stroke.

### Data collection and analysis

Two review authors applied the inclusion criteria, extracted data and assessed trial quality. We obtained both published and unpublished data if available

### Main results

We included four trials involving 350 patients. Not all trials contributed data to each outcome. The trials tested either intra-arterial urokinase or recombinant pro-urokinase versus an open control. One trial used guidewire-mediated clot disruption in some patients randomised to the intervention group. Most data came from trials that started treatment up to six hours after stroke; one small trial

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**Percutaneous vascular interventions for acute ischaemic stroke (Review)**

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started treatment up to a median of 12.5 hours after stroke. Most data came from trials of middle cerebral artery territory infarction. Compared with non-thrombolytic standard medical treatment, the intervention administered up to six hours after ischaemic stroke significantly increased the proportion of patients with favourable outcome (modified Rankin 0 to 2) three months after stroke (relative risk (RR) 1.47, 95% confidence interval (CI) 1.07 to 2.02). The intervention also significantly increased the risk of symptomatic intracranial haemorrhage within 24 hours of treatment (RR 3.85, 95% CI 0.91 to 16.36). There was no significant heterogeneity between the included trials.

### Authors' conclusions

Overall, intervention results in a significant increase in the proportion of patients with a favourable outcome, despite a significant increase in intracranial haemorrhage. Further trials are needed to confirm or refute these findings and, given the cost and practical difficulties, to establish whether percutaneous techniques are feasible and cost effective in wider clinical practice.

## PLAIN LANGUAGE SUMMARY

### Percutaneous vascular interventions for acute ischaemic stroke

The majority of disabling strokes are due to blockage of a large artery in the brain by a blood clot. For these patients, the most intuitive means of treatment is removal of the blockage by either injecting clot-dissolving (thrombolytic) drugs directly into the clot or removal of the 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 with poorer outcomes. This review of four trials involving 350 participants indicated that this form of treatment can remove large artery blood clots and improve the chances of good recovery despite an increased risk of bleeding in the brain. Long term risk of death is unaffected. However, it is still not clear what the time window is within which treatment is beneficial, what types of arterial blockage are most likely to respond, whether mechanical devices are effective, and whether any of these treatments are better than standard intravenous thrombolytic drugs. More information is needed from forthcoming randomised trials to answer these questions.

## BACKGROUND

Acute ischaemic stroke is a major cause of death and disability worldwide (Warlow 2003). The usual mechanisms are cerebral thrombosis and embolism. The prompt administration of intravenous thrombolytic drugs to selected patients has been shown to be beneficial (Wardlaw 2009) and is now used as routine medical treatment in those patients. The rapidly developing field of interventional radiology currently offers a variety of alternative approaches to recanalisation in acute ischaemic stroke. Case series have provided some feasibility and safety data (Brekenfeld 2005; Nedeltchev 2006) but they cannot provide evidence of efficacy. We therefore aimed to perform a systematic review of all randomised controlled trials (RCTs) in this field.

## OBJECTIVES

The objective of this review was to assess whether percutaneous vascular interventions plus medical treatment are superior to medical treatment alone for brain infarction.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials comparing percutaneous vascular interventions plus medical treatment to medical treatment alone in patients with acute ischaemic stroke. Intravenous thrombolytic treatment was permissible only when the same intravenous thrombolytic treatment was given to both the intervention group and the control group.

#### Types of participants

Patients with a definite acute ischaemic stroke (that is computerised tomography (CT) or magnetic resonance imaging (MRI) must have excluded cerebral haemorrhage).

## Types of interventions

All percutaneous arterial endovascular techniques aimed at revascularisation in acute ischaemic stroke, including but not confined to:

- angioplasty;
- 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 percutaneous interventions. Intravenous thrombolytic treatment was permissible only when the same intravenous thrombolytic treatment was also given to the control group.

## 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 outcome measure

Favourable functional outcome at the end of the scheduled follow-up period defined as a modified Rankin scale 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 patients in each individual modified Rankin scale category. If the modified Rankin scale score was not reported, we used the trial's definition of functional outcome.

### Secondary outcome measures

1. Deaths from all causes, both: (a) during the acute phase, i.e. first seven to 10 days, and (b) at the end of scheduled follow-up.
2. All intracranial haemorrhages and symptomatic intracranial haemorrhage within the acute phase (non-fatal or fatal). We defined symptomatic intracranial haemorrhage according to both the National Institute of Neurological Disorders and Stroke (NINDS) study (NINDS 1995) and European Cooperative Acute Stroke Study (ECASS) (Hacke 1995) criteria. When symptomatic intracranial haemorrhage was not reported according to these criteria, we considered using the trial's definition.

3. Degree of revascularisation, according to Higashida (Higashida 2003) and using the AOL score and the TIMI score (Khatri 2005).
4. Neurological status at end of follow-up.
5. Impairments at end of follow-up, e.g. Barthel Index score.
6. Major extracranial haemorrhage in the acute phase.

## Search methods for identification of studies

See the 'Specialized register' section in the [Cochrane Stroke Group](#) module.

1. We searched the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor in May 2010. We also searched the Trials Register of the Cochrane Peripheral Vascular Diseases Group (last searched May 2010).

2. In addition, we searched the following electronic databases from 1980 (the earliest publications in this field date from the 1980s). We adapted the MEDLINE search strategy for the other databases.

- i) Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 5).
- ii) MEDLINE (from 1980 to May 2010) ([Appendix 1](#)).
- iii) EMBASE (from 1980 to May 2010) ([Appendix 2](#)).
- iv) Science Citation Index (from 1980 to May 2010).
- v) ISI Proceedings (from 1990 to May 2010).
- vi) LILACS (Latin American and Caribbean Health Sciences Literature, 1982 to May 2010).
- vii) ACP journal club (<http://www.acpjc.org>) (last searched May 2010).
- viii) Database of Abstracts of Reviews of Effects (DARE) (<http://www.crd.york.ac.uk/crdweb>) (last searched May 2010).
- ix) ProQuest Dissertations & Theses (PQDT) (<http://proquest.umi.com/login>) (last searched May 2010).
- x) British Library Theses Service (<http://www.bl.uk/britishthesis>) (last searched May 2010).
- xi) National Research Register Archive (<http://portal.nih.ac.uk/Pages/NRRArchive.aspx>) (last searched May 2010).

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

- i) screened reference lists of relevant trials;
- ii) contacted the manufacturers of any interventional radiological equipment included in the review. We received replies from CoAxia Inc, phenox GmbH, EKOS Corporation, Boston Scientific, and Concentric Medical Inc;
- iii) contacted professional organisations in neuroradiology and interventional radiology and authors and researchers active in the field. We received replies from Raul Nogueira MD, Takashi Inoue MD, Malcolm McLeod PhD, Helmi L Lutsep MD, Alfonso Ciccone MD, Peter Rothwell PhD, and Chelsea Kidwell MD. We also received replies from the American Society of Neuroradiology and the British Society of Neuroradiology;

iv) handsearched the following journals from first available date, except those issues already searched on behalf of The Cochrane Collaboration and submitted to CENTRAL (<http://apps1.jhsph.edu/cochrane/masterlist.asp>):

a) *American Journal of Neuroradiology* (1990 to 2010),

b) *Brain* (1990 to 2010),

c) *Neuroradiology* (1990 to 2010),

d) *Stroke* (1990 to 2010);

v) searched the following ongoing trials registers (last searched May 2010):

a) Stroke Trials Registry (<http://www.strokecenter.org/trials>),

b) ClinicalTrials.gov (<http://www.clinicaltrials.gov>),

c) Current Controlled Trials (<http://www.controlled-trials.com>);

vi) searched conference proceedings for the World Federation of Interventional and Therapeutic Neuroradiology (2009);

vii) searched Google Scholar.

We searched for trials in all languages and arranged for translation of trial reports published in languages other than English.

## Data collection and analysis

### Selection of studies

Two review authors (KOR and EB) independently screened titles and abstracts of references identified by the searches. We obtained full paper copies of those trial reports which, from the title and abstract, appeared to be eligible for inclusion. The same two review authors then independently assessed these for inclusion. The review authors resolved any disagreements by discussion, with input from a third review author (PK) when needed. When a trial was excluded, we kept a record of both the report and the reason for exclusion.

### Quality assessment

Two review authors (KOR 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 2008):

1. adequate sequence generation;

2. allocation concealment;

3. blinding: in trials of percutaneous vascular interventions it is not possible to blind either the participants or those providing the interventions. However, outcome assessors can be blinded. In

this review, we defined blinding as 'yes', 'no', or 'unclear' as it pertained to blinding of outcome assessors;

4. incomplete outcome data addressed: we considered intention-to-treat analysis (ITT) adequate when (a) patients were analysed in the groups to which they were randomised regardless of what treatment they received, and (b) when the numbers of patients lost to follow-up and the associated reasons were reported;

5. free of selective reporting;

6. 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 2008).

### Data extraction

Two review authors (KOR 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 magnetic resonance imaging (MRI) diffusion/perfusion mismatch, computerised tomography (CT) angiography, or CT perfusion were used to identify eligible patients;

- time interval from onset to randomisation;

- time to actual delivery of percutaneous vascular therapy (not start of procedure);

- numbers of patients in each treatment group with outcome events;

- modality of percutaneous vascular intervention used;

- precise form of comparison therapy used.

One review author (KOR) entered the data into the Cochrane Review Manager software, RevMan 5.0 (RevMan 2008). These were checked by another review author (CW) against the hard copy 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 industrial sponsors concerned.

### Data synthesis

We analysed the data using the Cochrane Review Manager software, RevMan 5.0 (RevMan 2008). Two review authors (KOR and CW) independently conducted data analysis and resolved any disagreements by discussion. The appropriate statistical analysis was a binary logistic regression. We selected the Mantel-Haenszel method in view of both the relatively small size of the included trials and the relatively low event rates. We also aimed to carry out an ordinal logistic regression.

We estimated heterogeneity between trials' results using the  $I^2$  statistic (Higgins 2002). There was no statistically significant heterogeneity between the trials included in this review and we

therefore deemed a fixed-effect meta-analysis appropriate. We performed subgroup analyses using the methodology described by Deeks et al (Deeks 2001) as recommended in section 18.4.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

## RESULTS

### Description of studies

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

We included four trials (PROACT 1 1998; PROACT 2 1999; AUST 2005; MELT 2007) in which a total of 356 patients were randomised. Data on 350 patients were available for inclusion in the review. This is because functional outcome data for six patients who were randomised but not treated were not included in the PROACT 1 1998 trial publication and were otherwise unavailable.

### Types and severities of strokes included

Three trials (PROACT 1 1998; PROACT 2 1999; MELT 2007) screened patients with middle cerebral artery territory strokes. AUST 2005 screened patients with posterior circulation strokes. See [Characteristics of included studies](#) table.

### Age and gender of included patients

The mean age of patients in the treatment group in PROACT 1 1998 was 66 years, and in the control group 69 years. The mean age of patients in the treatment and control groups in PROACT 2 1999 and AUST 2005 was 64 years. The mean age of patients in the treatment and control groups in MELT 2007 was 67 years. Across the four included studies, 124 out of a total of 212 patients randomised to the treatment groups were men (58%), and 85 out of a total of 138 patients randomised to the control groups were men (61%). More men than women were randomised to the treatment groups in the PROACT 1 1998 and PROACT 2 1999 trials (14 out of 24 treatment patients versus 5 out of 14 control patients in PROACT 1 1998 were men; 70 out of 121 treatment versus 36 out of 59 control patients in PROACT 2 1999 were men). In AUST 2005, three out of eight patients in the treatment group were men, whereas seven out of eight patients in the control group were men. No gender imbalance was evident between the treatment and control groups in MELT 2007.

### Medical histories

There was little information available regarding the background medical information for patients in PROACT 1 1998 and MELT 2007. In PROACT 2 1999, conventional vascular risk factors were well balanced among the treatment and control groups, except for a significant excess of diabetic patients in the control group: 16 of 121 patients in the treatment group versus 18 of 59 patients in the control group ( $\text{Chi}^2$  7.7,  $\text{df} = 1$ ,  $P < 0.005$ ). In AUST 2005, conventional vascular risk factors were well balanced among the treatment and control groups.

### Mechanism

The predominant mechanisms of stroke in the included studies were: (1) cardioembolic, (2) carotid atheroembolism, and (3) unknown. Lacunar infarcts were not excluded. The proportion of cardiogenic strokes in PROACT 1 1998 was 54% in the treatment arm and 64% in the control arm, and in PROACT 2 1999 60% in the treatment arm and 51% in the control arm. The proportion of cardiogenic strokes was much higher in MELT 2007 (88% in the treatment arm and 83% in the control arm). In AUST 2005, given the exclusive selection of posterior circulation strokes it can be assumed that the mechanisms were cardioembolic, vertebrobasilar atheroembolism, or unknown.

### Visible infarction on the CT scan at randomisation

In PROACT 1 1998 patients with CT abnormalities that were consistent with early ischaemia were included, comprising 23 out of 40 randomised patients. In five of these 23 patients, the area of CT ischaemia was greater than one-third of the middle cerebral artery territory. All of these five patients were allocated to the treatment group and all developed haemorrhagic transformation within 24 hours. In PROACT 2 1999, patients with hypodense changes or sulcal effacement involving more than one-third of the territory of the middle cerebral artery were excluded (ECASS CT criterion). Early ischaemic changes were present in 125 out of 180 randomised patients, and the ECASS CT criterion was violated in 14 of these 125 patients. Of the 14 cases where the ECASS CT criterion was violated, 12 were allocated to the treatment group. Therefore, a total of 17 patients from PROACT 1 1998 and PROACT 2 1999 were randomised to treatment in violation of the ECASS CT criterion, representing 8% of the total number of patients randomised to treatment across the four included studies. Any bias introduced by this factor would be expected to dilute any favourable treatment effect and increase the rate of intracerebral haemorrhage in the treatment group.

Patients were not excluded from AUST 2005 on the basis of baseline ischaemic CT abnormalities. 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. These CT abnormalities were present in 54 out of a total of 114 randomised patients (47%).

### Time to randomisation

In [PROACT 1 1998](#) and [PROACT 2 1999](#) the protocol specified randomisation and initiation of treatment within six hours of onset of symptoms. The time to randomisation in [PROACT 1 1998](#) was unclear. The time to actual delivery of percutaneous vascular therapy (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.

It was clear that the patients in [MELT 2007](#) were randomised earlier than the patients in [PROACT 1 1998](#) and [PROACT 2 1999](#). This constituted a potential source of bias towards more favourable outcome in the [MELT 2007](#) patients compared to the [PROACT 1 1998](#) and [PROACT 2 1999](#) patients.

### Drug, dosage, and means of drug delivery

There were differences between the PROACT trials ([PROACT 1 1998](#); [PROACT 2 1999](#)) and [MELT 2007](#) in terms of the dose, form, and method of drug delivery. See [Characteristics of included studies](#) table.

### Mechanical clot disruption

Mechanical clot disruption was prohibited by the protocol in [PROACT 1 1998](#) and [PROACT 2 1999](#) and did not occur in [AUST 2005](#). In [MELT 2007](#) mechanical clot disruption with a guidewire was permitted and was performed in 39 patients in the treatment group.

### Concomitant use of antithrombotic treatment

The protocol for concomitant antithrombotic therapy varied from trial to trial. There was likely to have been an imbalance in the antithrombotic therapy given to the treatment and control groups in [PROACT 1 1998](#), where safety concerns prompted an alteration of the concomitant antithrombotic regime 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 terms of outcome, the direction of any bias introduced by these imbalances is unknown.

### Assessment of outcome

All trials reported mortality data at the end of follow-up. For one trial ([MELT 2007](#)) data were available for deaths in the acute phase. Assessment of primary functional outcome was by means

of the modified Rankin scale in all four included trials. A potential source of bias was the fact that [PROACT 1 1998](#), which comprised 11% of the total number of patients, did not report the outcome in terms of modified Rankin scale 0 to 2. All four included trials reported Barthel Index outcome data for activities of daily living. Three trials ([PROACT 1 1998](#); [PROACT 2 1999](#), [MELT 2007](#)) reported neurological outcome data in the form of the NIHSS. The method of determination of intracranial haemorrhage was variable and is listed in the [Characteristics of included studies](#) table.

Two trials reported recanalisation using the TIMI classification ([PROACT 1 1998](#); [PROACT 2 1999](#)): TIMI grade 3 is complete flow in both M1 and M2 divisions of the middle cerebral artery, TIMI grade 2 is partial flow in either middle cerebral artery segment. One trial ([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. One trial ([AUST 2005](#)) did not pre-specify criteria for judging recanalisation, although recanalisation at day 7 to 10 was a pre-specified secondary outcome. Recanalisation was described as either complete or partial.

### Risk of bias in included studies

The quality of randomisation in included studies was variable. Blinding was considered likely to have been adequate in all included trials.

While no patients were lost to follow-up in any of the included trials, one trial ([PROACT 1 1998](#)) did not report intention-to-treat analyses and one trial ([AUST 2005](#)) did not report pre-specified secondary outcomes. Such selective reporting clearly conferred a risk of bias.

Three included trials ([PROACT 1 1998](#); [AUST 2005](#); [MELT 2007](#)) were terminated early and consequently suffered from a lack of statistical power. For details, see [Characteristics of included studies](#) table.

### Effects of interventions

#### Functional outcome at the end of follow-up

For modified Rankin score 0 to 2, data were available for a total of 310 randomised patients from three trials ([PROACT 2 1999](#); [AUST 2005](#); [MELT 2007](#)). There was an overall significant effect in favour of treatment (relative risk (RR) 1.47, 95% confidence interval (CI) 1.07 to 2.02,  $P = 0.02$ ) with very little between-study heterogeneity ( $I^2 = 0\%$ ,  $P = 0.47$ ) ([Analysis 1.1](#)). For modified Rankin score 0 to 1, data were available for a total of 350 randomised patients from four trials ([PROACT 1 1998](#); [PROACT 2 1999](#); [AUST 2005](#); [MELT 2007](#)). There was an overall highly

significant effect in favour of treatment (RR 1.73, 95% CI 1.17 to 2.57,  $P = 0.006$ ) with very little between-study heterogeneity ( $I^2 = 0\%$ ,  $P = 0.74$ ) (Analysis 1.2).

### Deaths from all causes during follow-up

Data were available for a total of 350 randomised patients from four trials (PROACT 1 1998; PROACT 2 1999; AUST 2005; MELT 2007). There was no evidence of an effect on death from all causes in the treatment group (RR 0.89, 95% CI 0.60 to 1.33,  $P = 0.58$ ) with very little between-study heterogeneity ( $I^2 = 0\%$ ,  $P = 0.80$ ) (Analysis 2.1).

### Deaths from all causes during the acute phase

Data were available for a total of 114 patients from a single trial (MELT 2007). There was no evidence of an effect on death from all causes in the acute phase in the treatment group (RR 5.00, 95% CI 0.25 to 101.89,  $P = 0.30$ ) (Analysis 2.2).

### Symptomatic intracranial haemorrhage during the first 24 hours

Data were available for a total of 202 randomised patients from two trials (PROACT 1 1998; PROACT 2 1999). There was a non-significant trend towards excess risk of symptomatic intracerebral haemorrhage in the treatment group (RR 3.85, 95% CI 0.91 to 16.36,  $P = 0.07$ ) with very little between-study heterogeneity ( $I^2 = 0\%$ ,  $P = 0.52$ ) (Analysis 3.1).

### Symptomatic intracranial haemorrhage at the end of follow-up

Data were available for a total of 40 randomised patients from a single trial (PROACT 1 1998). Whilst there was no evidence of an excess risk of intracerebral haemorrhage in the treatment group (RR 1.08, 95% CI 0.22 to 5.17,  $P = 0.93$ ), the confidence intervals were wide and could not exclude the possibility of a substantial excess (Analysis 3.2).

### Recanalisation

TIMI recanalisation data were available for a total of 198 randomised patients from the PROACT 1 1998 and PROACT 2 1999 trials. For TIMI grade 3, there was an overall significant effect in favour of treatment (RR 8.25, 95% CI 1.63 to 41.90,  $P = 0.01$ ) with very little between-study heterogeneity ( $I^2 = 0\%$ ,  $P = 0.81$ ) (Analysis 4.1). When data for TIMI grade 2 and 3 were examined there was an overall very significant effect in favour of treatment (RR 4.02, 95% CI 2.32 to 6.95,  $P < 0.00001$ ) with negligible between-study heterogeneity ( $I^2 = 0\%$ ,  $P = 0.99$ ) (Analysis 4.2).

### All intracranial haemorrhage during the first 24 hours

Data were available for a total of 202 randomised patients from two trials (PROACT 1 1998; PROACT 2 1999). There was an overall highly significant excess risk of intracranial haemorrhage in the treatment group (RR 3.11, 95% CI 1.56 to 6.18,  $P = 0.001$ ) with very little between-study heterogeneity ( $I^2 = 0\%$ ,  $P = 0.46$ ) (Analysis 5.1).

### All intracranial haemorrhage at the end of follow-up

Data were available for a total of 154 randomised patients from two trials (PROACT 1 1998; MELT 2007). There was a significant excess risk of intracerebral haemorrhage in the treatment group (RR 1.46, 95% CI 1.01 to 2.11,  $P = 0.04$ ) with very little between-study heterogeneity ( $I^2 = 0\%$ ,  $P = 0.91$ ) (Analysis 5.2).

### Neurological outcome at the end of follow-up

A NIHSS score of 0 to 1 was taken to signify good neurological outcome. NIHSS data were available for a total of 334 randomised patients from three trials (PROACT 1 1998; PROACT 2 1999; MELT 2007). There was a very significant effect in favour of treatment (RR 2.03, 95% CI 1.21 to 3.40,  $P = 0.007$ ) with very little between-study heterogeneity ( $I^2 = 0\%$ ,  $P = 0.65$ ) (Analysis 6.1).

### Activities of daily living at the end of follow-up

A Barthel index (BI) score of 90 or greater was taken to signify a good outcome in terms of activities of daily living. Barthel index data were available for a total of 334 randomised patients from three trials (PROACT 1 1998; PROACT 2 1999; MELT 2007). There was no clear evidence of an effect of treatment on activities of daily living (RR 1.24, 95% CI 0.94 to 1.65,  $P = 0.13$ ), with very little between-study heterogeneity ( $I^2 = 0\%$ ,  $P = 0.98$ ) (Analysis 7.1).

### Major extracranial haemorrhage in the acute phase

In PROACT 1 1998 two patients had severe injection site haemorrhages but the allocation of these patients was unclear. No patients in MELT 2007 had major extracranial haemorrhages in the acute phase. It was unclear whether any patients in PROACT 2 1999 or AUST 2005 had major extracranial haemorrhages in the acute phase.

### Subgroup analyses and sensitivity analyses

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

## DISCUSSION

This systematic review acquired data on a comparatively small total of 350 patients. Most of these data pertain to the effect of intra-arterial thrombolysis in middle cerebral artery territory strokes, since mechanical intervention was performed in a minority of patients randomised to the intervention group in one trial and posterior circulation strokes affected only a minority of patients. On the basis of these data, there is evidence that intra-arterial thrombolytic treatment results in higher rates of recanalisation than non-thrombolytic standard medical care, and that this effect translates into significantly improved functional outcome at three-months follow-up.

These benefits are gained despite a significantly increased rate of all intracranial haemorrhage within 24 hours of treatment. While data for case fatality within the first two weeks following treatment are too sparse for reliable conclusions to be drawn, it is reassuring that overall case fatality at the end of follow-up remains unchanged.

Systematic reviews are not immune from bias and a number of possible sources need to be taken into account. Imbalances in baseline covariates potentially related to outcome after thrombolysis can arise through chance in trials with low statistical power. Given the evidence that women respond more favourably to thrombolysis than men (Kent 2005), the overall excess of women in the treatment group compared to the control group may have exaggerated the overall treatment effect. The excess of diabetic patients in the PROACT 2 1999 control group would also be expected to render the treatment group more likely to respond favourably to thrombolysis (Caso 2007). The trials included in this review were balanced with respect to other factors associated with improved response to thrombolytic treatment (Demchuk 2001; Hacke 2004).

There was no evidence of publication bias. The search delivered a total of eight published studies, of which only one (PROACT 2 1999) was positive in terms of its primary outcome. While low statistical power and premature termination affected many of these trials, it is clear that this was not a barrier to publication. The ability to make appropriate use of such data is a strength of systematic review. Indeed, our meta-analyses benefit from a very low degree of heterogeneity ( $I^2 = 0$ ), strengthening the likelihood that a single true effect is being measured in each case.

The applicability of percutaneous vascular interventions is limited by the particular training and skills required and by the high costs of the associated drugs, devices and infrastructure. One difficulty in terms of interpreting these data for the purposes of routine

clinical practice is that pro-urokinase and urokinase are not currently available. The practice of intra-arterial thrombolysis using alternative thrombolytic agents such as tissue plasminogen activator (tPA) relies on non-randomised data (Nedeltchev 2006). Data from ongoing randomised controlled trials of intra-arterial tPA are therefore needed in order to definitively establish the role of intra-arterial thrombolysis in clinical practice, and also to evaluate alternative percutaneous vascular interventions such as mechanical devices. Further trials are needed comparing percutaneous vascular interventions with intravenous thrombolytic therapy.

## AUTHORS' CONCLUSIONS

### Implications for practice

Current data are insufficient to establish the role of percutaneous vascular intervention for acute ischaemic stroke in clinical practice.

### Implications for research

Data from forthcoming randomised trials will be required in order to confirm these findings and to establish:

- the effects of various forms of percutaneous vascular intervention (different thrombolytic drugs, different mechanical devices);
- the optimal time window for the use of percutaneous vascular intervention;
- the differential responsiveness of patient subgroups to percutaneous vascular intervention.

Trials comparing percutaneous vascular interventions to intravenous thrombolytic treatment (for example Synthesis Expansion) are also required.

## ACKNOWLEDGEMENTS

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## REFERENCES

### References to studies included in this review

#### AUST 2005 *{published and unpublished data}*

Macleod M, Davis S, Mitchell P, Gerraty RP, Fitt G, Hankey GJ, et al. Results of a multicentre, randomised controlled trial of intra-arterial urokinase in the treatment of acute posterior circulation ischaemic stroke. *Cerebrovascular Diseases* 2005;**20**:12–7.

#### MELT 2007 *{published and unpublished data}*

Ogawa A, Mori E, Minematsu K, Taki W, Takahashi A, Nemoto S, et al. Randomised trial of intra-arterial infusion of urokinase within 6 hours of middle cerebral artery stroke. *Stroke* 2007;**38**:2633–9.

#### PROACT 1 1998 *{published data only (unpublished sought but not used)}*

del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M, et al. PROACT: A phase II trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. *Stroke* 1998;**29**:4–11.

#### PROACT 2 1999 *{published data only (unpublished sought but not used)}*

Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial pro-urokinase for acute ischaemic stroke: the PROACT II study: a randomised controlled trial. *JAMA* 1999;**282**:2003–11.

### References to studies excluded from this review

#### Ducroq 2005 *{published data only}*

Ducroq X, Bracard S, Taillandier L, Anxionnat R, Lacour JC, Guillemin F, et al. Comparison of intravenous and intra-arterial urokinase thrombolysis for acute ischaemic stroke. *Journal of Neuroradiology* 2005;**32**:26–32.

#### Keris 2001 *{published data only}*

Keris V, Rudnicka S, Vorona V, Enina G, Tilgale B, Fricbergs J. Combined intra-arterial/intravenous thrombolysis for acute ischemic stroke. *American Journal of Neuroradiology* 2001;**22**:352–8.

#### Lewandowski 1999 *{published data only}*

Lewandowski CA, Frankel M, Tomsick TA, Broderick J, Frey J, Clark W, et al. Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) bridging trial. *Stroke* 1999;**30**:2598–605.

#### Wolfe 2008 *{published data only}*

Wolfe T, Suarez JI, Tarr RW, Welter E, Landis D, Sunshine JL, et al. Comparison of combined venous and arterial thrombolysis with primary arterial therapy using recombinant tissue plasminogen activator in acute ischemic stroke. *Journal of Stroke and Cerebrovascular Diseases* 2008;**17**:121–8.

### References to ongoing studies

#### IMS 3 *{published data only}*

Interventional Management of Stroke Trial 3. [www.ims3.org](http://www.ims3.org).

#### MR CLEAN *{published data only}*

MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands. Netherlands Trial Register (<http://www.trialregister.nl>).

#### MR RESCUE *{published data only}*

MR RESCUE: MR and Recanalization of Stroke Clots Using Embolectomy. [www.strokecenter.org/trials/TrialDetail.aspx?tid=559](http://www.strokecenter.org/trials/TrialDetail.aspx?tid=559).

#### SENTIS *{published data only}*

SENTIS: Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke. <http://www.strokecenter.org/trials/TrialDetail.aspx?tid=618>.

#### THRACE *{published data only}*

THRACE: Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke. <http://clinicaltrials.gov/ct2/show/NCT01062698>.

#### THRUST *{published data only}*

THRUST. [www.acutestroke.org/modules.php?op=modload&name=News&file=article&sid=92](http://www.acutestroke.org/modules.php?op=modload&name=News&file=article&sid=92).

### Additional references

#### Brekenfeld 2005

Brekenfeld C, Remonda L, Nedeltchev K, V Bredow F, Ozdoba C, Wiest R, et al. Endovascular neuroradiological treatment of acute ischaemic stroke: techniques and results in 350 patients. *Neurological Research* 2005;**27** Suppl 1: 29–35.

#### Caso 2007

Caso V, Paciaroni M, Venti M, Palmerini F, Silvestrelli G, Milia P, et al. Determinants of outcome in patients eligible for thrombolysis in ischaemic stroke. *Vascular Health and Risk Management* 2007;**3**:749–54.

#### Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG editor(s). *Systematic Reviews in Health Care: Meta-analysis in Context*. 2nd Edition. London: BMJ Publication Group, 2001.

#### Demchuk 2001

Demchuk A, Tanne D, Hill M, Kasner SE, Hanson S, Grond M, et al. Predictors of good outcome after intravenous tPA for acute ischaemic stroke. *Neurology* 2001;**57**:474–80.

#### Hacke 1995

Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995;**274**:1017–25.

**Hacke 2004**

Hacke W, Donnan G, Feicht C, Kaste M, von Kummer R, Broderick JP, et al. Association of outcome with early stroke treatment: pooled analysis of ALTANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004;**363**:768–74.

**Higashida 2003**

Higashida R, Furlan A. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke* 2003;**34**:e109–37.

**Higgins 2002**

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**:1539–58.

**Higgins 2008**

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).

**Kent 2005**

Kent DM, Price LL, Ringleb P, Hill MD, Selker HP. Sex-based differences in response to tissue plasminogen activator in acute ischaemic stroke: a pooled analysis of randomised clinical trials. *Stroke* 2005;**36**:62–5.

**Khatri 2005**

Khatri P, Neff J, Broderick J, et al. Revascularization end points in stroke interventional trials: recanalization versus

reperfusion in IMS-I. *Stroke* 2005;**36**:2400–3.

**Nedeltchev 2006**

Nedeltchev K, Fischer U, Arnold M, Ballinari P, Haefeli T, Kappeler L, et al. Long-term effect of intra-arterial thrombolysis in stroke. *Stroke* 2006;**37**:3002–7.

**NINDS 1995**

The NINDS rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *New England Journal of Medicine* 1995;**333**:1581–7.

**RevMan 2008**

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

**Saver 2007**

Saver J. Intra-arterial fibrinolysis for acute ischaemic stroke. The message of Melt. *Stroke* 2007;**38**:2627–8.

**Wardlaw 2009**

Wardlaw J, Murray V, Berge E, del Zoppo G. Thrombolysis for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD000213]

**Warlow 2003**

Warlow C, Sudlow C, Dennis M, Sandercock P. Stroke. *Lancet* 2003;**362**:1211–24.

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### AUST 2005

Methods	Randomised, multicentre, controlled clinical trial
Participants	Patients with acute posterior circulation stroke considered to be due to occlusion of a major vessel were randomised when digital subtraction angiography of the posterior circulation showed a lesion judged to be lysable Glasgow Coma Scale $\geq 9$ Age 18 to 85 years
Interventions	Percutaneous vascular intervention (IA thrombolysis with UK) plus anticoagulation versus anticoagulation alone, within 24 hours of stroke onset. UK was given in increments of 100,000IU to a maximum of 1,000,000 IU. All patients received intra-arterial heparin as a 5000 IU 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 and Rankin scores) at 6 months Secondary outcomes: (1) recanalisation rate at 7 to 10 days; (2) neurological impairment at 6 months; (3) safety and tolerability of IA UK; (4) cost effectiveness of therapy
Notes	There was no clear definition of symptomatic intracerebral intracranial haemorrhage

#### *Risk of bias*

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomisation by telephone with a central office, and subsequently by the pharmacy department at the Royal Melbourne Hospital. In 2 cases patients were randomised by coin toss in the treating centre, a practice approved by the trial steering committee. Concealment of allocation is considered adequate in each case, but a lack of detail in relation 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?	Yes	
Blinding? All outcomes	Yes	All outcomes were determined by an independent outcomes committee blinded to treatment allocation. Clinical outcomes

AUST 2005 (Continued)

		were determined at 6 months by a certified research nurse or a neurologist blinded to treatment allocation and who was not involved in the patient's initial care
Incomplete outcome data addressed? All outcomes	Yes	No patients lost to clinical follow-up
Free of selective reporting?	No	Secondary outcomes not reported Baseline angiographic findings not reported for 2 patients No a priori requirement for follow-up imaging
Free of other bias?	Unclear	The trial was stopped early because of slow recruitment and the withdrawal from sale of UK

MELT 2007

Methods	Randomised, controlled, multicentre clinical trial
Participants	Acute middle cerebral artery territory ischaemic stroke allowing initiation of treatment within 6 hours of stroke onset Patients 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 middle cerebral artery NIHSS at least 5 Age 20 to 75 years
Interventions	IA thrombolysis with UK ± mechanical clot disruption with guidewire versus 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 UK 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: (1) sICH within 24 hours of starting treatment; (2) degree of recanalisation; (3) NIHSS score 0 to 1 at 24 hours, 30 days, 90 days; (4) Barthel Index score at least 95 at 30 days, 90 days; (5) mRS score 0 to 1 at 30 days, 90 days; (6) any haemorrhagic finding on CT
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 NINDS-defined sICH rates	
<b>Risk of bias</b>		
Item	Authors’ judgement	Description
Adequate sequence generation?	Unclear	Randomisation by a central randomisation centre via the Internet, but the precise methodology used for randomisation was not explained and its remains unclear whether sequence generation was adequate
Allocation concealment?	Yes	Central randomisation via Internet
Blinding? All outcomes	Yes	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 addressed? All outcomes	Yes	Intention-to-treat results presented 1 patient not randomised due to computer error No patients lost to follow-up
Free of selective reporting?	Yes	All pre-specified outcomes reported
Free of other bias?	Unclear	(1) The trial was stopped early by the steering committee following a recommendation by the independent monitoring committee when IV-tPA became available in Japan. This recommendation was that the trial be either modified so as not to include patients presenting within 3 hours of stroke onset, or terminated. This is not considered to have been a potential source of bias (2) No information provided regarding conventional vascular risk factors possibly related to outcome

**PROACT 1 1998**

Methods	Randomised, controlled, multicentre, phase II clinical trial
Participants	Acute middle cerebral artery 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

**PROACT 1 1998** (Continued)

	middle cerebral artery. NIHSS 4 to 30, but patients with isolated aphasia or hemianopia were also included Age 18 to 85 years
Interventions	IA thrombolysis with pro-UK versus no such treatment against a background of standard medical care not including IV-tPA. All patients 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 IU 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 period of infusion. The dose of rpro-UK was 6 mg
Outcomes	Primary efficacy outcome: recanalisation of M1 or M2 middle cerebral artery 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)
Notes	The protocol for follow-up imaging in this study and <a href="#">PROACT 2 1999</a> is unclear

***Risk of bias***

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Central randomisation centre assigned patients to the treatment or control groups, therefore concealment of allocation is considered adequate. However, the precise randomisation methodology was not explained and it remains unclear whether sequence generation was adequate
Allocation concealment?	Yes	Central randomisation
Blinding? All outcomes	Yes	All investigators and examining physicians were blinded to treatment assignment
Incomplete outcome data addressed? All outcomes	No	No patients lost to follow-up. This study did not report the primary efficacy outcome for 6 randomised but untreated patients, i.e. an on-treatment rather than the preferred intention-to-treat analysis. Of these 6 patients, 5 were in the treatment group, representing 16% of the total randomised treatment group; the remaining randomised but untreated patient was in

PROACT 1 1998 (Continued)

		the placebo group. Given the possibility that the 5 patients 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 patients, and it is therefore not considered that the safety analysis is prone to on-treatment bias. Any on-treatment bias due to these 6 patients will be diluted in the overall analysis
Free of selective reporting?	Yes	All pre-specified outcomes reported
Free of other bias?	Unclear	<p>(1) No information provided regarding conventional vascular risk factors possibly related to outcome</p> <p>(2) Trial stopped early by sponsor to determine whether there was sufficient evidence of safety and efficacy to support continuation of a longer term program, ultimately expressed in the form of the phase III <a href="#">PROACT 2 1999</a> trial. No safety concerns were involved in that decision. An analysis of the dataset 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 which are stopped for any reason other than according to specific pre-defined stopping rules are theoretically prone to bias. However, it is felt that it remains unclear whether this factor introduced any bias in this particular case</p>

PROACT 2 1999

Methods	Randomised, controlled, multicentre, phase III clinical trial
Participants	Acute middle cerebral artery 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

PROACT 2 1999 (Continued)

Interventions	IA thrombolysis with pro-UK versus no such treatment against a background of standard medical care not including IV-tPA. See <a href="#">PROACT 1 1998</a>	
Outcomes	<p>Primary outcome: favourable clinical outcome, defined as a mRS score of 0 to 2 at 3 months</p> <p>Secondary outcomes: (1) NIHSS 0 to 1 at 90 days; (2) rate of angiographic recanalisation; (3) at least 50% reduction in baseline NIHSS at 90 days; (4) Barthel Index scores of at least 60 and at least 90 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</p>	
Notes	Published analyses performed independently of the sponsor	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors’ judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	A computer-generated master randomisation schedule using a random block size was used for sequence generation
Allocation concealment?	Yes	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? All outcomes	Yes	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 addressed? All outcomes	Yes	Intention-to-treat results reported. Some patients carried forward. Some appropriate imputation used. No patients lost to follow-up
Free of selective reporting?	Yes	All pre-specified outcomes reported
Free of other bias?	No	Significant excess of diabetics in control group. This is a potential source of bias

CT: computerised tomography  
 IA: intra-arterial  
 IV-tPA: intravenous tissue plasminogen activator  
 mRS: modified Rankin Scale  
 NIHSS: National Institutes of Health Stroke Scale  
 rpro-UK: recombinant pro-urokinase  
 sICH: symptomatic intracerebral haemorrhage  
 UK: urokinase

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

Study	Reason for exclusion
Ducroq 2005	This is not a comparison of IA-tPA versus control, since only the control group is given IV-tPA
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	(1) This is not a comparison of IA-tPA versus control (no IA-tPA), since both groups receive IA-tPA (2) Control group given IA-tPA; this is not the protocol definition of 'routine medical treatment'
Wolfe 2008	(1) This is not a comparison of IA-tPA versus control (no IA-tPA), since both groups receive IA-tPA (2) Control group given IA-tPA; this 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]*

#### IMS 3

Trial name or title	Interventional Management of Stroke (IMS) III Trial
Methods	Phase III randomised, multicentre clinical trial
Participants	Acute ischaemic stroke, NIHSS at least 10 Age 18 to 80 years
Interventions	Patients receive either IV-tPA followed by percutaneous vascular intervention or IV-tPA alone (2:1 ratio). IV-tPA is given within 3 hours of stroke onset. Percutaneous vascular intervention must begin within 5 hours and be completed within 7 hours of stroke onset. The choice of percutaneous vascular intervention will be made by the treating neurointerventionalist from the following options: (1) the Merci thrombus-removal device, (2) infusion of tPA and delivery of low-intensity ultrasound at the site of the occlusion via the EKOS Micro-Infusion Catheter, (3) infusion of tPA via a standard micro-catheter

**IMS 3** (Continued)

Outcomes	<p>Primary efficacy outcome: favourable clinical outcome, defined as a mRS of 0 to 2 at 3 months</p> <p>Primary safety outcomes: mortality at 3 months and sICH within the first 30 hours after onset</p> <p>Secondary efficacy measures: (1) Barthel Index, Glasgow Outcome Scale, NIHSS, EuroQol EQ-5D, and Trail Making Test, Parts A and B at 3 months; (2) early response to treatment as determined by an NIHSS of 0 to 2 at 24 hours; (3) a CT angiography assessment of intracranial vascular patency at 24 hours (both treatment groups); (4) the volume of cerebral infarction as measured by a CT scan at 24 ± 6 hours from onset; (5) the rate of TICI Grade II or III perfusion flow and recanalisation of the primary arterial occlusion at completion of angiography (percutaneous vascular intervention group only)</p> <p>Secondary safety measures: (1) the proportion of participants with Type II parenchymal intracerebral hematomas within the first 36 hours; (2) the incidence of any asymptomatic haemorrhage within the first 24 hours</p>
Starting date	2006
Contact information	Ms Rose Beckmann, Administrative Research Associate Email: Beckmare@ucmail.uc.edu
Notes	354/900 participants recruited as of February 2010

**MR CLEAN**

Trial name or title	CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands
Methods	Phase III randomised, multicentre clinical trial Minimum age 18 years
Participants	Acute ischaemic stroke, NIHSS at least 2 Symptomatic intracranial proximal arterial occlusion demonstrated by CTA, MRA or TCD
Interventions	Percutaneous vascular intervention (tPA and/or mechanical thrombectomy) within 6 hours of onset versus no treatment against a background of optimal medical management including IV-tPA. The choice of percutaneous vascular intervention will be made by the treating neurointerventionalist
Outcomes	<p>Primary outcome: modified Rankin score at 90 days</p> <p>Secondary outcomes: (1) vessel recanalisation at 24 to 48 hours after treatment, assessed by CTA or MRA; (2) infarct size at 24 to 48 hours assessed by CT; (3) asymptomatic or symptomatic intracerebral haemorrhage at 24 to 48 hours assessed by CT</p>
Starting date	2010
Contact information	Dr D Dippel, Erasmus Medical Center Department of Neurology, Suite Ee 2240a, PO Box 2040, Rotterdam, The Netherlands Email: d.dippel@erasmusmc.nl, p.fransen@erasmusmc.nl
Notes	

**MR RESCUE**

Trial name or title	MR Imaging and REcanalisation of Stroke Clots Using Embolectomy
Methods	Phase II randomised, multicentre clinical trial
Participants	Acute ischaemic stroke, NIHSS at least 6. Large vessel proximal anterior circulation occlusion on MR or CT angiography (internal carotid, M1 or M2 MCA); percutaneous vascular intervention can be initiated within 8 hours from onset Age 18 to 85 years
Interventions	The Merci thrombus-removal device ± adjunctive tPA versus no treatment against a background of standard medical care not including IV-tPA Patients may receive adjunctive tPA after use of the retriever has been completed
Outcomes	Primary outcome: modified Rankin score at 90 days Secondary outcomes: additional clinical, angiographic, and MRI radiographic outcome measures
Starting date	2005
Contact information	Ms Gina Ramirez Email: gcr9@georgetown.edu
Notes	72/120 enrolled as of February 2010

**SENTIS**

Trial name or title	Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke trial
Methods	A phase III randomised, multicentre clinical trial Minimum age 18 years
Participants	Acute ischaemic stroke, NIHSS 5 to 18 Percutaneous vascular intervention can be initiated within 14 hours from onset
Interventions	NeuroFlo treatment plus standard medical management (American Stroke Association guidelines) versus standard medical management alone
Outcomes	Primary outcomes: efficacy as measured by neurological improvement; and safety as measured by serious adverse events at 90 days Secondary Outcomes: (1) acute improvement in neurological function 24 hours post-procedure; (2) hospital length of stay; (3) patient disposition upon discharge
Starting date	2005
Contact information	Ms Lori Austin, VP, Clinical Affairs, CoAxia Inc, 10900 73rd Ave N, Suite 102, Maple Grove, MN 55369, USA
Notes	500/500 enrolled as of March 2010

## THRACE

Trial name or title	Trial and cost-effectiveness evaluation of intra-arterial thrombectomy in acute ischaemic stroke
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 middle cerebral artery (M1) or the upper third of the basilar artery
Interventions	Treatment arm: standard IV thrombolysis alteplase (r-tPA)/Actilyse followed by mechanical thrombectomy (MERCİ, PENUMBRA, CATCH, SOLITAIRE) versus standard IV thrombolysis alone
Outcomes	Primary outcome: modified Rankin score at 90 days Secondary outcomes: quality of life (Euroqol EQ-5D) at 90 days, Barthel Score at 90 days
Starting date	2010
Contact information	Principal Investigator: Prof. Serge Bracard, Interventional Neuroradiology, Central Hospital Nancy, France (HNF) Email: s.bracard@chu-nancy.fr
Notes	

## THRUST

Trial name or title	THRombectomy in Unsuccessful Stroke Thrombolysis
Methods	Randomised multicentre clinical trial
Participants	Patients following unsuccessful IV-tPA defined as lack of improvement on the NIHSS after 2 hours compared with the results immediately before start of treatment CT angiography must confirm a retrievable occlusion Age range not available
Interventions	Thrombectomy using the MERCİ thrombus-removal device versus no intervention
Outcomes	No data currently available
Starting date	No data currently available
Contact information	SITS (Safe Implementation of Thrombolysis in Stroke) International, Karolinska Stroke Research, Department of Neurology, R2:03, Karolinska University Hospital, S-171 76 Stockholm, Sweden Email:sits.ico@acutestroke.org
Notes	

CT: computerised tomography

CTA: computed tomography angiography

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. Functional outcome at end of follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Functional outcome: mRS 0 to 2	3	310	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.07, 2.02]
2 Functional outcome: mRS 0 to 1	4	350	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [1.17, 2.57]

### Comparison 2. Case fatality (all cause)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Case fatality at end of follow-up	4	350	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.60, 1.33]
2 Case fatality within acute phase (first 2 weeks)	1	114	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 101.89]

### Comparison 3. Symptomatic intracranial haemorrhage (NINDS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic intracranial haemorrhage within 24 hours	2	202	Risk Ratio (M-H, Fixed, 95% CI)	3.85 [0.91, 16.36]
2 Symptomatic intracranial haemorrhage at the end of follow-up	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.22, 5.17]

### Comparison 4. Recanalisation rate at 120 minutes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recanalisation: TIMI grade 3	2	198	Risk Ratio (M-H, Fixed, 95% CI)	8.25 [1.63, 41.90]
2 Recanalisation: TIMI grade 2 and 3	2	198	Risk Ratio (M-H, Fixed, 95% CI)	4.02 [2.32, 6.95]

### Comparison 5. All intracranial haemorrhages

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All intracranial haemorrhages within 24 hours	2	202	Risk Ratio (M-H, Fixed, 95% CI)	3.11 [1.56, 6.18]
2 All intracranial haemorrhages at the end of follow-up	2	154	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.01, 2.11]

---

### Comparison 6. Good neurological outcome (NIHSS 0 to 1) at end of follow-up

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Good neurological outcome (NIHSS 0 to 1) at the end of follow-up	3	334	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.21, 3.40]

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### Comparison 7. Barthel Index at end of follow-up

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Barthel Index at least 90 at end of follow-up	3	334	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.94, 1.65]

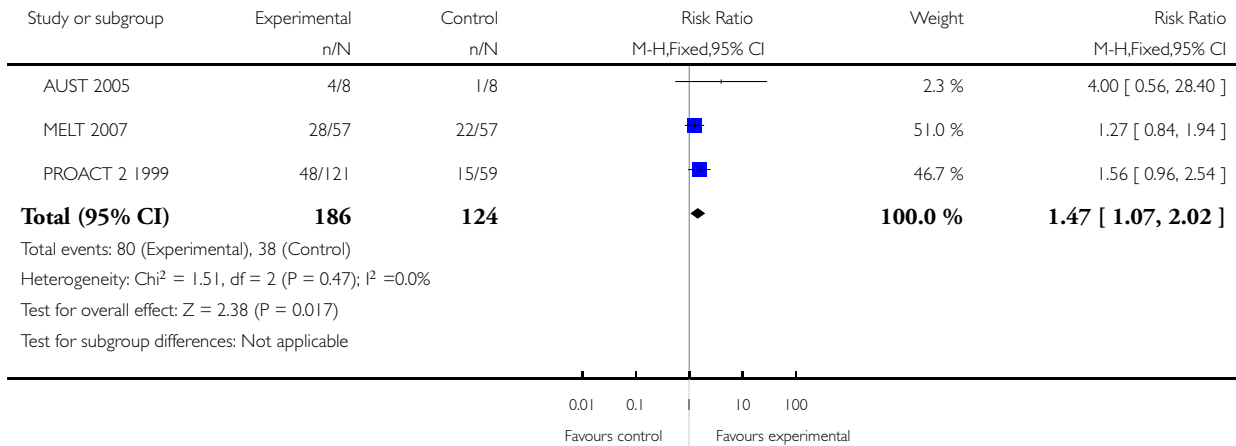
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**Analysis 1.1. Comparison 1 Functional outcome at end of follow-up, Outcome 1 Functional outcome: mRS 0 to 2.**

Review: Percutaneous vascular interventions for acute ischaemic stroke

Comparison: 1 Functional outcome at end of follow-up

Outcome: 1 Functional outcome: mRS 0 to 2

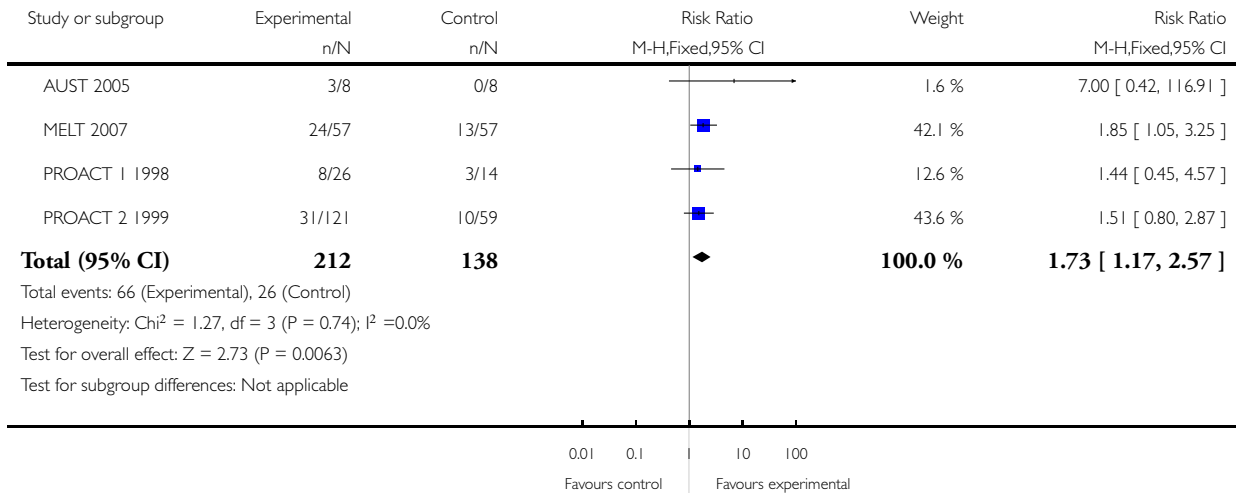


**Analysis 1.2. Comparison 1 Functional outcome at end of follow-up, Outcome 2 Functional outcome: mRS 0 to 1.**

Review: Percutaneous vascular interventions for acute ischaemic stroke

Comparison: 1 Functional outcome at end of follow-up

Outcome: 2 Functional outcome: mRS 0 to 1

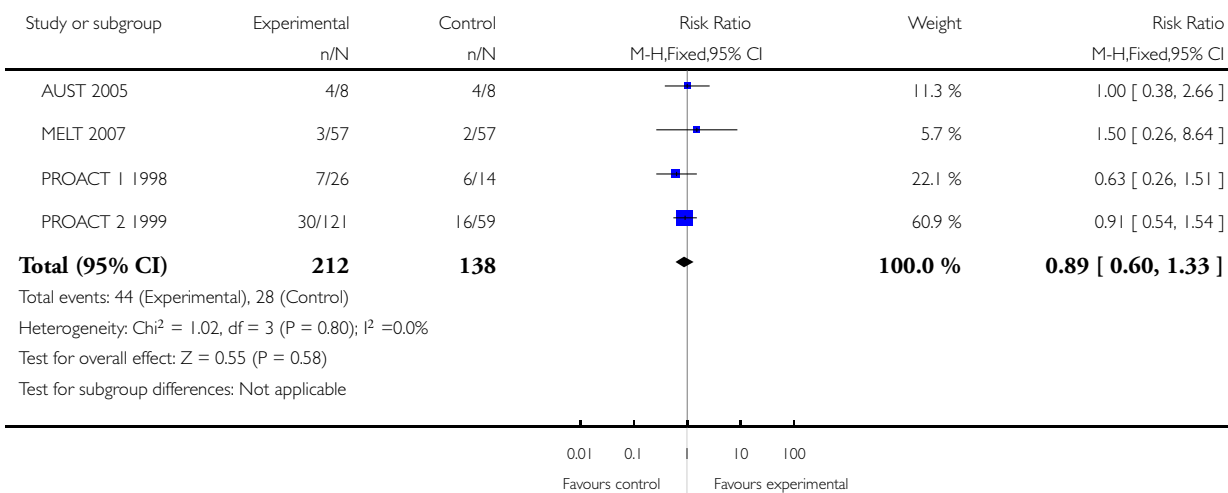


## Analysis 2.1. Comparison 2 Case fatality (all cause), Outcome 1 Case fatality at end of follow-up.

Review: Percutaneous vascular interventions for acute ischaemic stroke

Comparison: 2 Case fatality (all cause)

Outcome: 1 Case fatality at end of follow-up

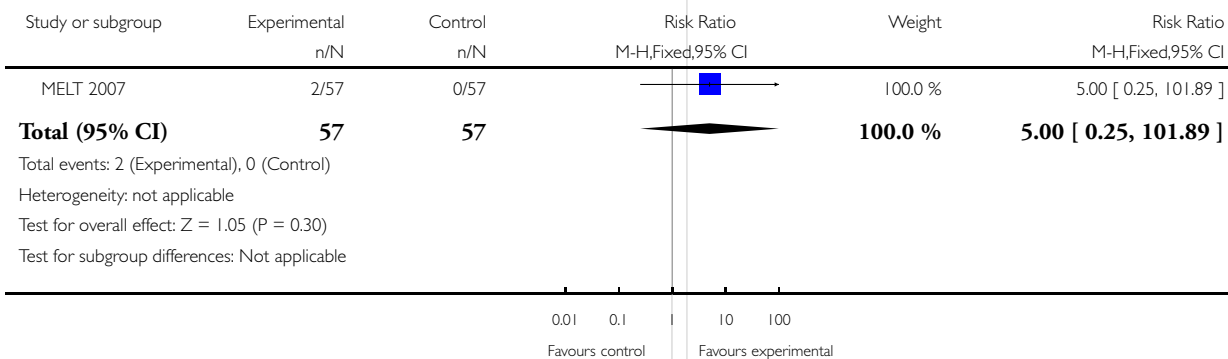


## Analysis 2.2. Comparison 2 Case fatality (all cause), Outcome 2 Case fatality within acute phase (first 2 weeks).

Review: Percutaneous vascular interventions for acute ischaemic stroke

Comparison: 2 Case fatality (all cause)

Outcome: 2 Case fatality within acute phase (first 2 weeks)

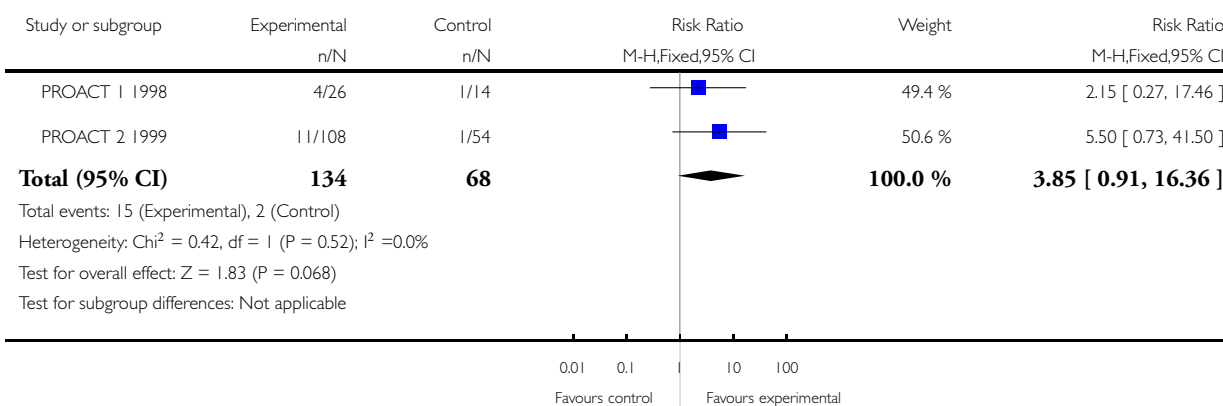


### Analysis 3.1. Comparison 3 Symptomatic intracranial haemorrhage (NINDS), Outcome 1 Symptomatic intracranial haemorrhage within 24 hours.

Review: Percutaneous vascular interventions for acute ischaemic stroke

Comparison: 3 Symptomatic intracranial haemorrhage (NINDS)

Outcome: 1 Symptomatic intracranial haemorrhage within 24 hours

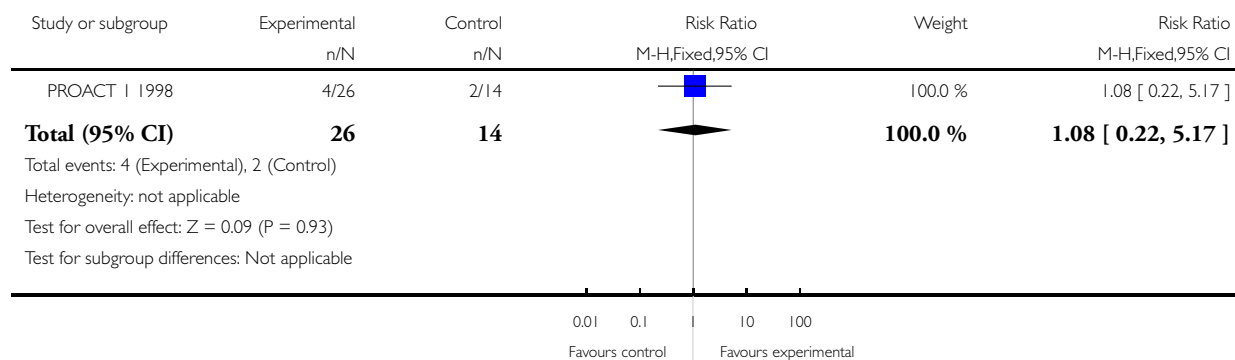


### Analysis 3.2. Comparison 3 Symptomatic intracranial haemorrhage (NINDS), Outcome 2 Symptomatic intracranial haemorrhage at the end of follow-up.

Review: Percutaneous vascular interventions for acute ischaemic stroke

Comparison: 3 Symptomatic intracranial haemorrhage (NINDS)

Outcome: 2 Symptomatic intracranial haemorrhage at the end of follow-up

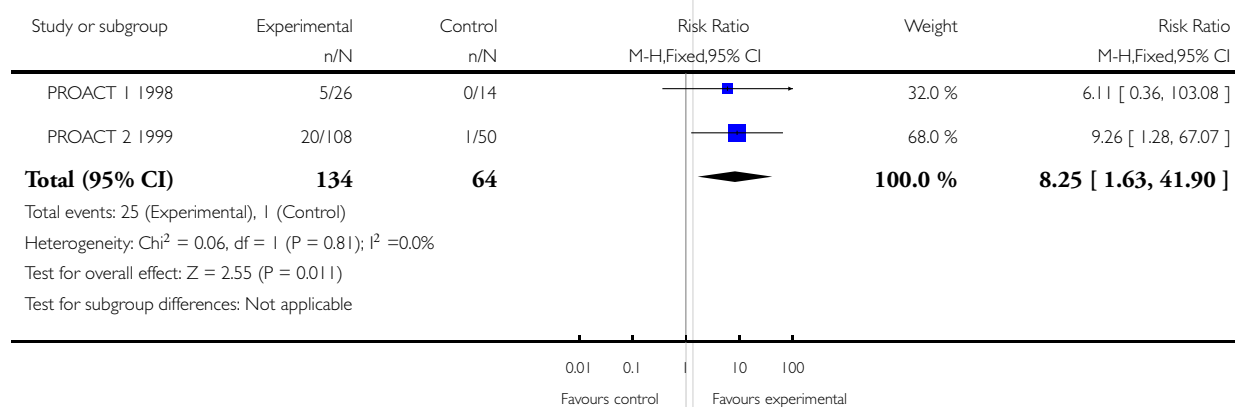


### Analysis 4.1. Comparison 4 Recanalisation rate at 120 minutes, Outcome 1 Recanalisation: TIMI grade 3.

Review: Percutaneous vascular interventions for acute ischaemic stroke

Comparison: 4 Recanalisation rate at 120 minutes

Outcome: 1 Recanalisation: TIMI grade 3

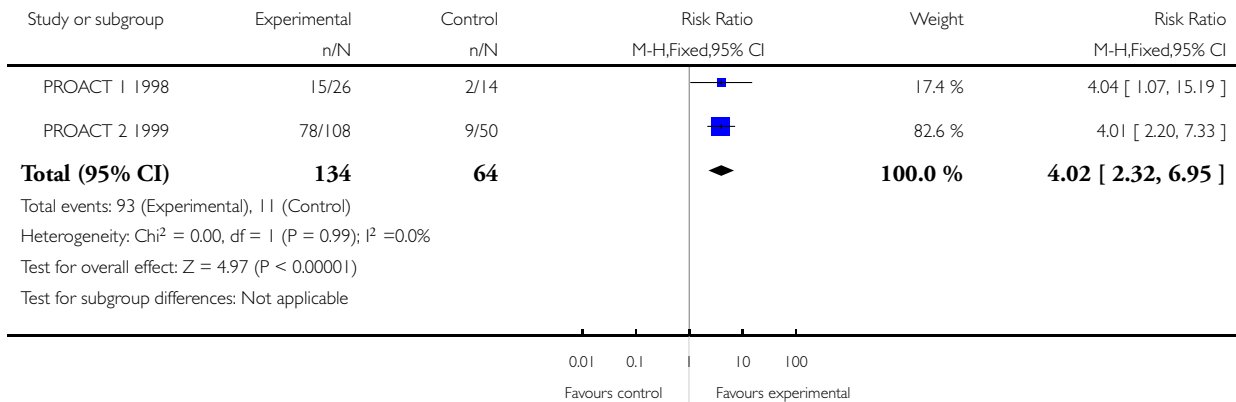


### Analysis 4.2. Comparison 4 Recanalisation rate at 120 minutes, Outcome 2 Recanalisation: TIMI grade 2 and 3.

Review: Percutaneous vascular interventions for acute ischaemic stroke

Comparison: 4 Recanalisation rate at 120 minutes

Outcome: 2 Recanalisation: TIMI grade 2 and 3

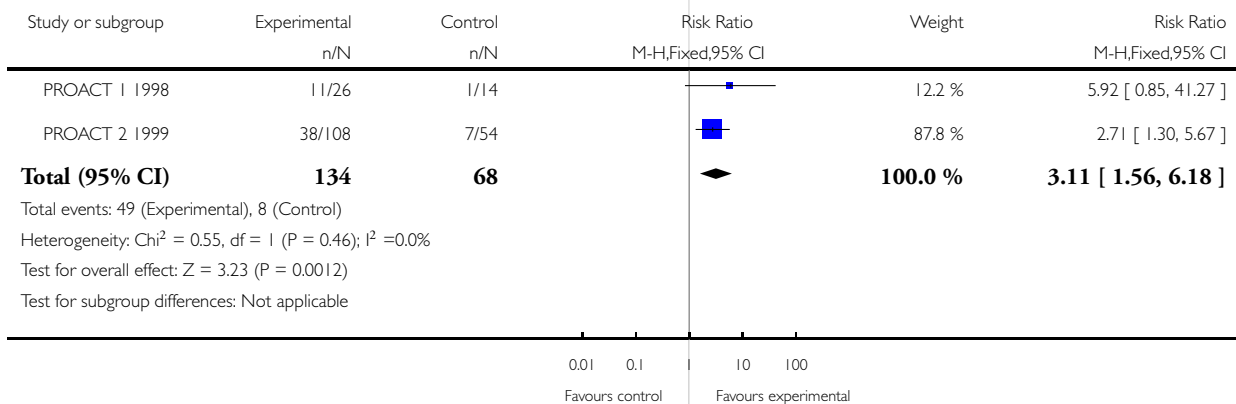


### Analysis 5.1. Comparison 5 All intracranial haemorrhages, Outcome 1 All intracranial haemorrhages within 24 hours.

Review: Percutaneous vascular interventions for acute ischaemic stroke

Comparison: 5 All intracranial haemorrhages

Outcome: 1 All intracranial haemorrhages within 24 hours

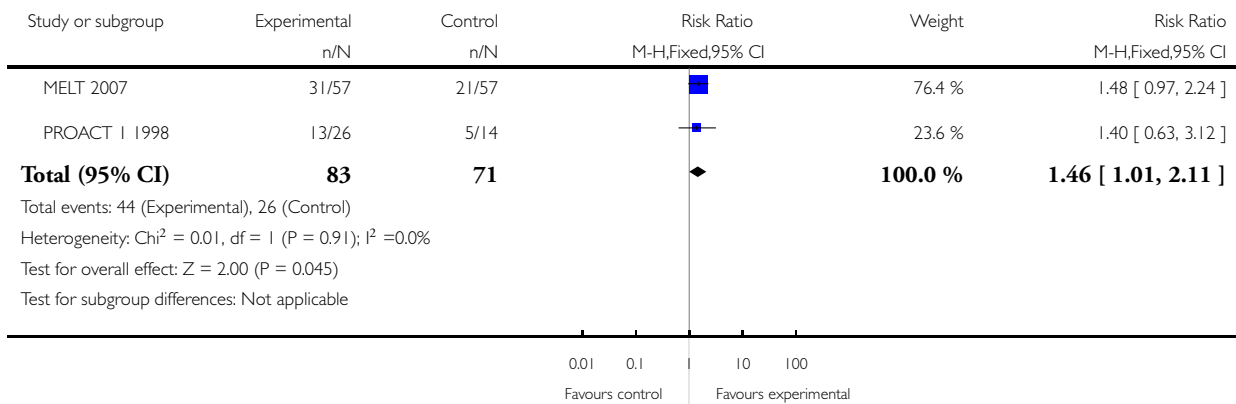


**Analysis 5.2. Comparison 5 All intracranial haemorrhages, Outcome 2 All intracranial haemorrhages at the end of follow-up.**

Review: Percutaneous vascular interventions for acute ischaemic stroke

Comparison: 5 All intracranial haemorrhages

Outcome: 2 All intracranial haemorrhages at the end of follow-up

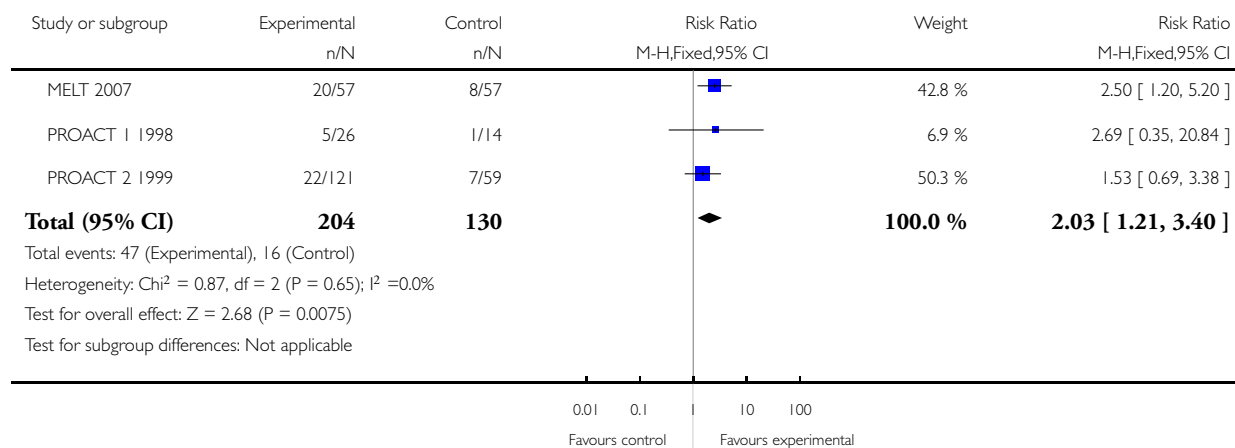


**Analysis 6.1. Comparison 6 Good neurological outcome (NIHSS 0 to 1) at end of follow-up, Outcome 1  
Good neurological outcome (NIHSS 0 to 1) at the end of follow-up.**

Review: Percutaneous vascular interventions for acute ischaemic stroke

Comparison: 6 Good neurological outcome (NIHSS 0 to 1) at end of follow-up

Outcome: 1 Good neurological outcome (NIHSS 0 to 1) at the end of follow-up

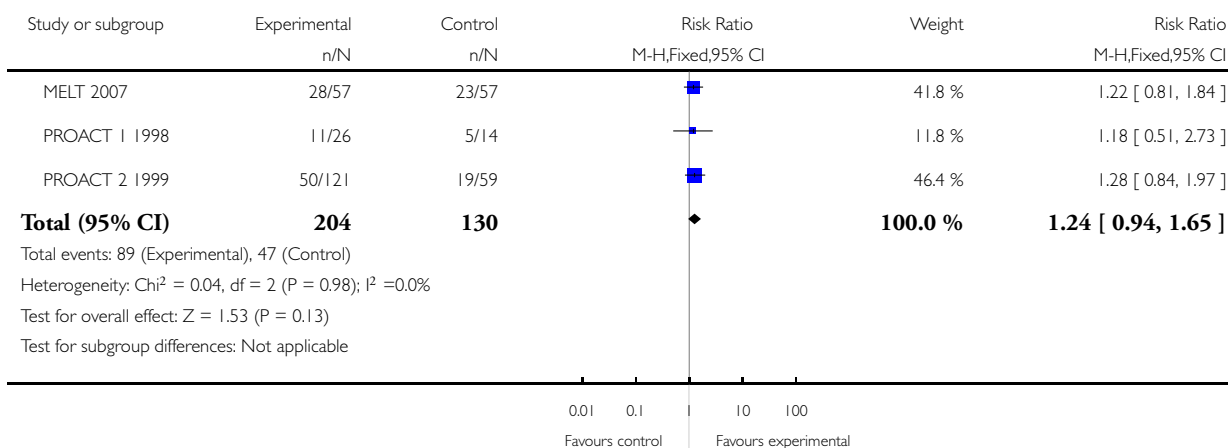


## Analysis 7.1. Comparison 7 Barthel Index at end of follow-up, Outcome 1 Barthel Index at least 90 at end of follow-up.

Review: Percutaneous vascular interventions for acute ischaemic stroke

Comparison: 7 Barthel Index at end of follow-up

Outcome: 1 Barthel Index at least 90 at end of follow-up



## APPENDICES

### Appendix I. 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 recanalization or clot lysis\$)).tw.
16. ((clot or thrombus or thrombi or embol\$) adj5 (aspirat\$ or remov\$ or retriev\$ or fragmentation or retract\$ or extract\$ or obliterate\$ 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 oclus\$ 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 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 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. fibrinolytic therapy/
26. fibrinolytic agent/ or plasmin/ or plasminogen/ or exp plasminogen activator/
27. blood clot lysis/
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. 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

## **HISTORY**

Protocol first published: Issue 1, 2009

Review first published: Issue 10, 2010

## **CONTRIBUTIONS OF AUTHORS**

KOR conducted the primary search of the literature and wrote the review. EB co-reviewed the results of the literature search and assisted with the writing of the review. CW provided statistical expertise. PK provided content expertise.

## **DECLARATIONS OF INTEREST**

None known

## **SOURCES OF SUPPORT**

### **Internal sources**

- No sources of support supplied

### **External sources**

- Health Research Board, Ireland.

KOR was supported by a Cochrane Fellowship Award from the Health Research Board of Ireland

## **DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

The protocol specified that percutaneous vascular intervention in the form of sonothrombolysis would be eligible for inclusion. Following discussion, it was clarified that sonothrombolysis would only be eligible for inclusion when delivered by intravascular means. The list of outcomes has been altered as follows.

1. Deaths attributable to stroke has been removed as an outcome.
2. Neurological outcome as measured by the National Institutes of Health Stroke Scale has been added.
3. Functional outcome as measured by the Barthel Index has been added.

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

Brain Ischemia [drug therapy; \*therapy]; Catheterization [\*methods]; Fibrinolytic Agents [\*administration & dosage]; Infarction, Middle Cerebral Artery [therapy]; Intracranial Hemorrhages [etiology]; Randomized Controlled Trials as Topic; Recombinant Proteins [administration & dosage]; Urokinase-Type Plasminogen Activator [administration & dosage]

### **MeSH check words**

Aged; Female; Humans; Male; Middle Aged