Percutaneous vascular interventions for acute ischaemic stroke (Review)

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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 We obtained both published and unpublished data if available.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
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:

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

All types of medical treatment could be given in addition to the 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 (NIHSDS 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 (Khatiri 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).
   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.acpj.org) (last searched May 2010).
   viii) Database of Abstracts of Reviews of Effects (DARE) (http://www.crd.york.ac.uk/criweb) (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/thesis) (last searched May 2010).
   xi) National Research Register Archive (http://portal.nihr.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 I² 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).

R E S U L T S

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

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 (Chi² 7.7, 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 out 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 (I² = 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**

The Cochrane Stroke Group editorial team for advice and support. Mrs Brenda Thomas for assistance in the design of the search strategy. Ms Angela Rice of the Library and Information Service, Mater Misericordiae University Hospital, Dublin, for advice and assistance in relation to the search strategies. Professor Timothy Lynch for facilities at the Dublin Neurological Institute. This review was originally envisaged by Professor Peter Sandercock.
REFERENCES

References to studies included in this review

AUST 2005  [published and unpublished data]

MELT 2007  [published and unpublished data]

PROACT 1 1998  [published data only (unpublished sought but not used)]

PROACT 2 1999  [published data only (unpublished sought but not used)]

References to studies excluded from this review

Ducroq 2005  [published data only]

Keris 2001  [published data only]

Lewandowski 1999  [published data only]

Wolfe 2008  [published data only]

References to ongoing studies

IMS 3  [published data only]

MR CLEAN  [published data only]

MR RESCUE  [published data only]

SENTIS  [published data only]

THRACE  [published data only]

THRUST  [published data only]

Additional references

Brekenfeld 2005

Caseo 2007

Deeks 2001

Demchuk 2001

Hache 1995
Hacke 2004

Higashida 2003

Higgins 2002

Higgins 2008

Kent 2005

Khatri 2005

Nedeltchev 2006

NINDS 1995

RevMan 2008

Saver 2007

Warlow 2003

* Indicates the major publication for the study
### Characteristics of included studies  
*ordered by study ID*

**AUST 2005**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised, multicentre, controlled clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>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 ≥ 9. Age 18 to 85 years.</td>
</tr>
<tr>
<td>Interventions</td>
<td>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.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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.</td>
</tr>
<tr>
<td>Notes</td>
<td>There was no clear definition of symptomatic intracerebral intracranial haemorrhage.</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>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.</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Yes</td>
<td>All outcomes were determined by an independent outcomes committee blinded to treatment allocation. Clinical outcomes</td>
</tr>
</tbody>
</table>
**AUST 2005** *(Continued)*

<table>
<thead>
<tr>
<th>Incomplete outcome data addressed?</th>
<th>Yes</th>
<th>No patients lost to clinical follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free of selective reporting?</td>
<td>No</td>
<td>Secondary outcomes not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline angiographic findings not re-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ported for 2 patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No a priori requirement for follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>imaging</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear</td>
<td>The trial was stopped early because</td>
</tr>
<tr>
<td></td>
<td></td>
<td>of slow recruitment and the withdrawal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>of UK</td>
</tr>
</tbody>
</table>

**MEL T 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.

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>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</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Central randomisation via Internet</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Yes</td>
<td>All angiograms were evaluated by the film reading committee, who were unaware of the clinical information</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical outcome was assessed by physicians unaware of the treatment allocation</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>Intention-to-treat results presented 1 patient not randomised due to computer error No patients lost to follow-up</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>All pre-specified outcomes reported</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear</td>
<td>(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</td>
</tr>
</tbody>
</table>

**PROACT 1 1998**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised, controlled, multicentre, phase II clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>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 carotid artery territory.</td>
</tr>
</tbody>
</table>
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 PROACT 2 1999 is unclear

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>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</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Central randomisation</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Yes</td>
<td>All investigators and examining physicians were blinded to treatment assignment</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>No</td>
<td>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</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Free of selective reporting?</th>
<th>Yes</th>
<th>All pre-specified outcomes reported</th>
</tr>
</thead>
</table>
| Free of other bias?         | Unclear | (1) No information provided regarding conventional vascular risk factors possibly related to outcome  
(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 PROACT 2 1999 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 |

PROACT 2 1999

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised, controlled, multicentre, phase III clinical trial</th>
</tr>
</thead>
</table>
| 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 |
Interventions

IA thrombolysis with pro-UK versus no such treatment against a background of standard medical care not including IV-tPA. See PROACT 1 1998

Outcomes

Primary outcome: favourable clinical outcome, defined as a mRS score of 0 to 2 at 3 months

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

Notes

Published analyses performed independently of the sponsor

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>A computer-generated master randomisation schedule using a random block size was used for sequence generation</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>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</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Yes</td>
<td>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</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Yes</td>
<td>Intention-to-treat results reported. Some patients carried forward. Some appropriate imputation used. No patients lost to follow-up</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>All pre-specified outcomes reported</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Significant excess of diabetics in control group. This is a potential source of bias</td>
</tr>
</tbody>
</table>
Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ducroq 2005</td>
<td>This is not a comparison of IA-tPA versus control, since only the control group is given IV-tPA</td>
</tr>
<tr>
<td>Keris 2001</td>
<td>This is not a comparison of IA-tPA versus control, since the intervention group received both IV-tPA and IA-tPA</td>
</tr>
</tbody>
</table>
| 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

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Interventional Management of Stroke (IMS) III Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Phase III randomised, multicentre clinical trial</td>
</tr>
</tbody>
</table>
| 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

**Outcomes**

<table>
<thead>
<tr>
<th>Primary efficacy outcome: favourable clinical outcome, defined as a mRS of 0 to 2 at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary safety outcomes: mortality at 3 months and sICH within the first 30 hours after onset</td>
</tr>
<tr>
<td>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)</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

**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**

Primary outcome: modified Rankin score at 90 days
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

**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**

18 Percutaneous vascular interventions for acute ischaemic stroke (Review)
## MR RESCUE

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>MR Imaging and REcanalisation of Stroke Clots Using Embolectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Phase II randomised, multicentre clinical trial</td>
</tr>
<tr>
<td>Participants</td>
<td>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</td>
</tr>
<tr>
<td>Interventions</td>
<td>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</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome: modified Rankin score at 90 days Secondary outcomes: additional clinical, angiographic, and MRI radiographic outcome measures</td>
</tr>
<tr>
<td>Starting date</td>
<td>2005</td>
</tr>
<tr>
<td>Contact information</td>
<td>Ms Gina Ramirez Email: <a href="mailto:gcr9@georgetown.edu">gcr9@georgetown.edu</a></td>
</tr>
<tr>
<td>Notes</td>
<td>72/120 enrolled as of February 2010</td>
</tr>
</tbody>
</table>

## SENTIS

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>A phase III randomised, multicentre clinical trial Minimum age 18 years</td>
</tr>
<tr>
<td>Participants</td>
<td>Acute ischaemic stroke, NIHSS 5 to 18 Percutaneous vascular intervention can be initiated within 14 hours from onset</td>
</tr>
<tr>
<td>Interventions</td>
<td>NeuroFlo treatment plus standard medical management (American Stroke Association guidelines) versus standard medical management alone</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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</td>
</tr>
<tr>
<td>Starting date</td>
<td>2005</td>
</tr>
<tr>
<td>Contact information</td>
<td>Ms Lori Austin, VP, Clinical Affairs, CoAxia Inc, 10900 73rd Ave N, Suite 102, Maple Grove, MN 55369, USA</td>
</tr>
<tr>
<td>Notes</td>
<td>500/500 enrolled as of March 2010</td>
</tr>
</tbody>
</table>
## THRACE

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Trial and cost-effectiveness evaluation of intra-arterial thrombectomy in acute ischaemic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised multicentre clinical trial</td>
</tr>
</tbody>
</table>
| 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 (MERCI, 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

CT: computerised tomography  
CTA: computed tomography angiography

## THRUST

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>THRombectomy in Unsuccessful Stroke Thrombolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised multicentre clinical trial</td>
</tr>
</tbody>
</table>
| 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 MERCI 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

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Percutaneous vascular interventions for acute ischaemic stroke (Review)  
Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
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

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

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

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

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

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

### Comparison 4. Recanalisation rate at 120 minutes

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Recanalisation: TIMI grade 3</td>
<td>2</td>
<td>198</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>8.25 [1.63, 41.90]</td>
</tr>
<tr>
<td>2 Recanalisation: TIMI grade 2 and 3</td>
<td>2</td>
<td>198</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>4.02 [2.32, 6.95]</td>
</tr>
</tbody>
</table>
### Comparison 5. All intracranial haemorrhages

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

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

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

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

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Barthel Index at least 90 at end of follow-up</td>
<td>3</td>
<td>334</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.24 [0.94, 1.65]</td>
</tr>
</tbody>
</table>
**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: Functional outcome at end of follow-up

Outcome: Functional outcome: mRS 0 to 2

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUST 2005</td>
<td>4/8</td>
<td>1/8</td>
<td>2.3 % 4.00 [0.56, 28.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELT 2007</td>
<td>28/57</td>
<td>22/57</td>
<td>51.0 % 1.27 [0.84, 1.94]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROACT 2 1999</td>
<td>48/121</td>
<td>15/59</td>
<td>46.7 % 1.56 [0.96, 2.54]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>186</strong></td>
<td><strong>124</strong></td>
<td><strong>100.0 % 1.47 [1.07, 2.02]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 80 (Experimental), 38 (Control)

Heterogeneity: Chi² = 1.51, df = 2 (P = 0.47); I² = 0.0%

Test for overall effect: Z = 2.38 (P = 0.017)

Test for subgroup differences: Not applicable
### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUST 2005</td>
<td>3/8</td>
<td>0/8</td>
<td>1.6 %</td>
<td>7.00</td>
<td>[0.42, 116.91]</td>
</tr>
<tr>
<td>MELT 2007</td>
<td>24/57</td>
<td>13/57</td>
<td>42.1 %</td>
<td>1.85</td>
<td>[1.05, 3.25]</td>
</tr>
<tr>
<td>PROACT 1 1998</td>
<td>8/26</td>
<td>3/14</td>
<td>12.6 %</td>
<td>1.44</td>
<td>[0.45, 4.57]</td>
</tr>
<tr>
<td>PROACT 2 1999</td>
<td>31/121</td>
<td>10/59</td>
<td>43.6 %</td>
<td>1.51</td>
<td>[0.80, 2.87]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**: 212/138 = 100.0 % 1.73 [1.17, 2.57]

Total events: 66 (Experimental), 26 (Control)

Heterogeneity: Chi$^2$ = 1.27, df = 3 (P = 0.74); I$^2$ = 0.0%

Test for overall effect: Z = 2.73 (P = 0.0063)

Test for subgroup differences: Not applicable

---

Percutaneous vascular interventions for acute ischaemic stroke (Review)

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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: Case fatality (all cause)

Outcome: Case fatality at end of follow-up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUST 2005</td>
<td>4/8</td>
<td>4/8</td>
<td>11.3 % 1.00 [ 0.38, 2.66 ]</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>MELT 2007</td>
<td>3/57</td>
<td>2/57</td>
<td>5.7 % 1.50 [ 0.26, 8.64 ]</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>PROACT 1 1998</td>
<td>7/26</td>
<td>6/14</td>
<td>22.1 % 0.63 [ 0.26, 1.51 ]</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>PROACT 2 1999</td>
<td>30/121</td>
<td>16/59</td>
<td>60.9 % 0.91 [ 0.54, 1.54 ]</td>
<td>100.0</td>
<td>0.89 [ 0.60, 1.33 ]</td>
</tr>
</tbody>
</table>

Total (95% CI) 212 138 100.0 % 0.89 [ 0.60, 1.33 ]

Total events: 44 (Experimental), 28 (Control)
Heterogeneity: Chi$^2$ = 1.02, df = 3 (P = 0.80); I$^2$ =0.0%
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable

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: Case fatality (all cause)

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELT 2007</td>
<td>2/57</td>
<td>0/57</td>
<td>100.0 % 5.00 [ 0.25, 101.89 ]</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 57 57 100.0 % 5.00 [ 0.25, 101.89 ]

Total events: 2 (Experimental), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.05 (P = 0.30)
Test for subgroup differences: Not applicable
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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>PROACT 1 1998</td>
<td>4/26</td>
<td>1/14</td>
<td>49.4 %</td>
<td>2.15 [ 0.27, 17.46 ]</td>
<td></td>
</tr>
<tr>
<td>PROACT 2 1999</td>
<td>11/108</td>
<td>1/54</td>
<td>50.6 %</td>
<td>5.50 [ 0.73, 41.50 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>134</strong></td>
<td><strong>68</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>3.85 [ 0.91, 16.36 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 15 (Experimental), 2 (Control)
Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² =0.0%
Test for overall effect: Z = 1.83 (P = 0.068)
Test for subgroup differences: Not applicable
### Analysis 3.2. Comparison 3 Symptomatic intracranial haemorrhage (NINDS), Outcome 2 Symptomatic intracranial haemorrhage at the end of follow-up.

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROACT 1 1998</td>
<td>4/26</td>
<td>2/14</td>
<td>1.08 [0.22, 5.17]</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>26</strong></td>
<td><strong>14</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.08 [0.22, 5.17]</strong></td>
</tr>
</tbody>
</table>

Total events: 4 (Experimental), 2 (Control)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.09 (P = 0.93)  
Test for subgroup differences: Not applicable

### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROACT 1 1998</td>
<td>5/26</td>
<td>0/14</td>
<td>6.11 [0.36, 103.08]</td>
<td>32.0%</td>
<td></td>
</tr>
<tr>
<td>PROACT 2 1999</td>
<td>20/108</td>
<td>1/50</td>
<td>9.26 [1.28, 67.07]</td>
<td>68.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>134</strong></td>
<td><strong>64</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>8.25 [1.63, 41.90]</strong></td>
</tr>
</tbody>
</table>

Total events: 25 (Experimental), 1 (Control)  
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² =0.0%  
Test for overall effect: Z = 2.55 (P = 0.01)  
Test for subgroup differences: Not applicable
### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROACT 1 1998</td>
<td>15/26</td>
<td>2/14</td>
<td>17.4 % 4.04 [ 1.07, 15.19 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROACT 2 1999</td>
<td>78/108</td>
<td>9/50</td>
<td>82.6 % 4.01 [ 2.20, 7.33 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>134</strong></td>
<td><strong>64</strong></td>
<td>100.0 % 4.02 [ 2.32, 6.95 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 93 (Experimental), 11 (Control)
Heterogeneity: $\chi^2 = 0.00$, df = 1 ($P = 0.99$); $I^2 = 0.0$
Test for overall effect: $Z = 4.97$ ($P < 0.00001$)
Test for subgroup differences: Not applicable

### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROACT 1 1998</td>
<td>11/26</td>
<td>1/14</td>
<td>12.2 % 5.92 [ 0.85, 41.27 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROACT 2 1999</td>
<td>38/108</td>
<td>7/54</td>
<td>87.8 % 2.71 [ 1.30, 5.67 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>134</strong></td>
<td><strong>68</strong></td>
<td>100.0 % 3.11 [ 1.56, 6.18 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 49 (Experimental), 8 (Control)
Heterogeneity: $\chi^2 = 0.55$, df = 1 ($P = 0.46$); $I^2 = 0.0$
Test for overall effect: $Z = 3.23$ ($P = 0.0012$)
Test for subgroup differences: Not applicable
**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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>MELT 2007</td>
<td>31/57</td>
<td>21/57</td>
<td>76.4 %</td>
<td>1.48 [ 0.97, 2.24 ]</td>
<td></td>
</tr>
<tr>
<td>PROACT 1 1998</td>
<td>13/26</td>
<td>5/14</td>
<td>23.6 %</td>
<td>1.40 [ 0.63, 3.12 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>83</strong></td>
<td><strong>71</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.46 [ 1.01, 2.11 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 44 (Experimental), 26 (Control)

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0.0%

Test for overall effect: Z = 2.00 (P = 0.045)

Test for subgroup differences: Not applicable

---

Percutaneous vascular interventions for acute ischaemic stroke (Review)

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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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELT 2007</td>
<td>20/57</td>
<td>8/57</td>
<td>42.8 %</td>
<td>2.50 [ 1.20, 5.20 ]</td>
<td></td>
</tr>
<tr>
<td>PROACT 1 1998</td>
<td>5/26</td>
<td>1/14</td>
<td>6.9 %</td>
<td>2.69 [ 0.35, 20.84 ]</td>
<td></td>
</tr>
<tr>
<td>PROACT 2 1999</td>
<td>22/121</td>
<td>7/59</td>
<td>50.3 %</td>
<td>1.53 [ 0.69, 3.38 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>204</strong></td>
<td><strong>130</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>2.03 [ 1.21, 3.40 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 47 (Experimental), 16 (Control)

Heterogeneity: $\chi^2 = 0.87$, df = 2 ($P = 0.65$); $I^2 = 0.0$

Test for overall effect: $Z = 2.68$ ($P = 0.0075$)

Test for subgroup differences: Not applicable
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: Barthel Index at end of follow-up

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>MELT 2007</td>
<td>28/57</td>
<td>23/57</td>
<td>41.8 %</td>
<td>1.22 [ 0.81, 1.84 ]</td>
<td></td>
</tr>
<tr>
<td>PROACT 1 1998</td>
<td>11/26</td>
<td>5/14</td>
<td>11.8 %</td>
<td>1.18 [ 0.51, 2.73 ]</td>
<td></td>
</tr>
<tr>
<td>PROACT 2 1999</td>
<td>50/121</td>
<td>19/59</td>
<td>46.4 %</td>
<td>1.28 [ 0.84, 1.97 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>204</td>
<td>130</td>
<td>100.0 %</td>
<td>1.24 [ 0.94, 1.65 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 89 (Experimental), 47 (Control)
Heterogeneity: Chi² = 0.04, df = 2 (P = 0.98); I² =0.0%
Test for overall effect: Z = 1.53 (P = 0.13)
Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. MEDLINE search strategy

The following search strategy was used for MEDLINE (Ovid) and modified for other databases.
1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/ 2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemisphe r$ 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.
Appendix 2. EMBASE search strategy

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/ or stroke patient/ or stroke unit/  
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva$)).tw.  
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.  
4. 1 or 2 or 3  
5. interventional radiology/ or endovascular surgery/  
6. percutaneous transluminal angioplasty/ or angioplasty/ or laser angioplasty/ or catheterization/ or catheter ablation/ or balloon dilatation/ or exp atherectomy/  
7. stent/  
8. thrombectomy/ or exp percutaneous thrombectomy/ or embolectomy/  
9. artery prosthesis/  
10. cerebral revascularization/ or reperfusion/ or artery dilatation/ or recanalization/  
11. (interventional adj3 (radiolog$ or radiograph$ or neuroradiolog$)).tw.
12. (angioplast$ or stent$).tw.
13. (thrombectomy or embolectomy or atherect$).tw.
14. thromboaspiration.tw.
15. ((mechanical or radiolog$ or pharmacomechanical or laser or endovascular or neurovascular) adj5 (thrombolys$ or reperfusion or fragmentation or aspiration or recanaliz$ or clot lys$)).tw.
16. ((clot or thrombus or thrombi or embol$) adj5 (aspirat$ or remov$ or retriev$ or fragmentation or retract$ or extract$ or obliterat$ or dispers$)).tw.
17. ((retrieval or extraction) adj5 device$).tw.
18. endoluminal repair$.tw.
19. ((blood vessel or artery) adj5 (prosthesis or implantat$)).tw.
20. ((merci or concentric) adj retriever).tw.
21. (endovascular snare$ or neuronet or microsnare or X-ciser or angiojet).tw.
22. ultrasound/ or exp ultrasound therapy/ or echography/ or doppler echography/ or intravascular ultrasound/
23. (ultrasound$ or ultrasonic$ or ultrasonogra$ or sonograp h$ 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. (thrombolys$ or fibrinoly$ or recanaliz$ or recanaliz$ or sonolys$).tw.
30. ((clot or thrombus) adj5 (lyse or lysis or dissolve$ or dissolution or fragment$)).tw.
31. (t-PA or t-PA or rt-PA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
32. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or pro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase).tw.
33. (sonothrombolysis or sonothromboly$ 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$).tw.
53. ((sing$ 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

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- No sources of support supplied

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- Health Research Board, Ireland.
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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