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Recanalisation therapies for wake-up stroke (Review)

Roaldsen MB, Lindekleiv H, Mathiesen EB, Berge E

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[Intervention Review]

Recanalisation therapies for wake-up stroke

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ABSTRACT

Background

About one in five strokes occur during sleep (wake-up stroke). People with wake-up strokes have traditionally been considered ineligible for thrombolytic treatment because the time of stroke onset is unknown. However, some studies suggest that these people may benefit from recanalisation therapies.

Objectives

To assess the effects of intravenous thrombolysis and other recanalisation therapies versus control in people with acute ischaemic stroke presenting on awakening.

Search methods

We searched the Cochrane Stroke Group Trials Register (last search: 9 January 2018). In addition, we searched the following electronic databases in December 2017: Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 11) in the Cochrane Library, MEDLINE, Embase, US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), the ISRCTN registry, and Stroke Trials Registry. We also screened references lists of relevant trials, contacted trialists, undertook forward tracking of relevant references, and contacted manufacturers of relevant devices and equipment.

Selection criteria

Randomised controlled trials of intravenous thrombolytic drugs or intra-arterial therapies in people with acute ischaemic stroke presenting upon awakening.

Data collection and analysis

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 We obtained both published and unpublished data.

Main results

We included one pilot trial with nine participants. The trial was a feasibility trial that included participants with an unknown onset of stroke and signs on perfusion computed tomography of ischaemic tissue at risk of infarction, who were randomised to alteplase (0.9 mg/kg) or placebo. One trial was prematurely terminated due to signs of efficacy of the intervention arm; we did not include this trial because we were not able to obtain data for the portion of the participants with wake-up stroke after requesting this information from the trial authors. We identified six ongoing trials.

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Authors' conclusions

There is insufficient evidence from randomised controlled trials for recommendations concerning recanalisation therapies for wake-up stroke. Results from ongoing trials will hopefully establish the efficacy and safety of such therapies.

PLAIN LANGUAGE SUMMARY

Recanalisation therapies for wake-up stroke

Review question: Do people who wake up with stroke benefit from treatments to reopen blood vessels (recanalisation therapies)?

Background: Most strokes are caused by a blockage of a blood vessel in the brain by a blood clot (ischaemic stroke), which are a leading cause of death and disability. Treatments to reopen blood vessels (such as clot-dissolving drugs or devices to remove blood clots) may improve recovery after ischaemic stroke if blood flow is rapidly restored.

About one in five strokes occur during sleep (wake-up stroke). People with wake-up stroke have traditionally been considered ineligible for recanalisation therapies because the time of stroke onset is unknown. However, some studies suggest that these people may benefit from recanalisation therapies.

Search date: We searched for randomised controlled trials (a type of experiment in which people are randomly allocated to one or more treatment groups) up until 9 January 2018.

Study characteristics: We included one trial with nine participants randomised to a recanalisation therapy or to placebo (dummy treatment). The trial was a feasibility study for perfusion computed tomography-guided thrombolysis in people with unknown onset of stroke.

Key results: There is insufficient evidence to determine if recanalisation therapies improve outcome in people with wake-up stroke. There are six ongoing trials that may contribute to our review when completed.

Quality of evidence: Low. There were insufficient data to assess the effect of treatment.

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Summary of findings for the main comparison. Recanalisation therapies compared to no recanalisation therapies for wake-up stroke

Recanalisation therapies compared to no recanalisation therapies for wake-up stroke

Patient or population: wake-up stroke
Setting: in-hospital
Intervention: recanalisation therapies
Comparison: no recanalisation therapies

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no recanalisation therapies	Risk with recanalisation therapies				
Independent functional outcome (mRS score 0 to 2) at end of follow-up - not reported	-	-	-	-	-	Too few participants for analysis
Symptomatic intracranial haemorrhage at 14 days follow-up - not reported	-	-	-	-	-	Too few participants for analysis
Dead at end of follow-up - not measured	-	-	-	-	-	Too few participants for analysis
Quality of life at end of follow-up	-	-	-	-	-	Too few participants for analysis
Neurological status at 7 to 14 days and at end of follow-up	-	-	-	-	-	Too few participants for analysis

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

CI: confidence interval; **mRS:** modified Rankin Scale

GRADE Working Group grades of evidence

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

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BACKGROUND

Acute ischaemic stroke is a major cause of death and disability worldwide (Lozano 2012). Intravenous thrombolysis and other recanalisation therapies may restore perfusion and improve clinical outcomes if given within a few hours after stroke onset (Wardlaw 2012).

Approximately one in five strokes occur during sleep (Bassetti 1999). Individuals with stroke symptoms presenting on awakening have traditionally been considered ineligible for thrombolytic treatment because the time of stroke onset is unknown. However, these people may benefit from thrombolytic treatment if the onset of stroke was shortly before awakening. Several studies suggest that the onset of stroke during sleep is close to awakening, and that people with wake-up stroke and people with stroke onset within 4.5 hours of waking share many clinical findings on brain imaging (Roveri 2011; Silva 2010). Registry studies suggest that intravenous thrombolysis is safe for people with wake-up stroke (Barreto 2009; Manawadu 2013; Meretoja 2010), but the efficacy and safety of intravenous thrombolysis and other recanalisation therapies in people with acute ischaemic stroke on awakening have not been established.

Other reviews have assessed the benefits of intravenous thrombolytic therapy and intra-arterial stroke therapy (O'Rourke 2010; Wardlaw 2012). However, the effects of recanalisation therapies in people with wake-up stroke may differ from those in people with stroke whilst awake because the onset of stroke in wake-up stroke is unknown and because changes in cerebral blood flow and metabolism occur during sleep (Madsen 1991).

We aimed to perform a systematic review of all randomised controlled trials of intravenous thrombolytic drugs and other recanalisation therapies versus control in people with acute ischaemic stroke presenting on awakening.

Description of the condition

Stroke is globally the second leading cause of death and the third leading cause of loss of disability-adjusted life-years (Lozano 2012; Murray 2012). Most strokes are caused by the blockage of an intracranial artery by a clot (ischaemic stroke).

Description of the intervention

Recanalisation therapies for acute ischaemic stroke include intravenous administration of thrombolytic drugs and intra-arterial therapies.

Thrombolytic drugs given intravenously are used most commonly and work by dissolving blood clots. These drugs include urokinase, recombinant pro-urokinase (rpro-UK), streptokinase (SK), and recombinant tissue plasminogen activator (rt-PA) including alteplase, duteplase, lumbrokinase, tenecteplase, reteplase, and desmoteplase. Alteplase is the only thrombolytic drug licenced to treat acute ischaemic stroke up to 4.5 hours after symptom onset. The recommended dose of alteplase is 0.9 mg per kilogram of body weight (maximum 90 mg), with 10% as a bolus and the rest infused intravenously over 60 minutes.

Intra-arterial therapies include administration of thrombolytic drugs through an intra-arterial catheter, mechanical thrombus disruption using a microcatheter or guidewire, angioplasty, and the use of endovascular devices. The benefit of mechanical thrombus disruption and endovascular devices is covered in another Cochrane Review (O'Rourke 2010). Our review differs from O'Rourke 2010 in that we also include intravenous thrombolysis and only people with wake-up stroke.

How the intervention might work

Interventions may restore perfusion to the ischaemic brain parenchyma, which may reduce damage to the brain parenchyma and improve clinical outcome.

Why it is important to do this review

Intravenous thrombolysis with alteplase is the only approved reperfusion drug therapy for acute ischaemic stroke. Currently, only a minority of people with stroke are treated because of strict inclusion criteria. Approximately one in five strokes occur during sleep; these people are ineligible for thrombolytic drug therapy because the time of stroke onset is unknown. However, they may benefit from reperfusion therapies if stroke onset was shortly before awakening.

The efficacy and safety of intravenous thrombolytic drugs and intra-arterial treatments in people with acute ischaemic stroke upon awakening have not been established. If recanalisation therapies are shown to provide any benefit for such individuals, the proportion of people with stroke who might benefit from such treatments may be increased.

OBJECTIVES

To assess the effects of intravenous thrombolysis and other recanalisation therapies versus control in people with acute ischaemic stroke presenting on awakening.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials of intravenous thrombolytic drugs or intra-arterial therapies versus control in people with acute ischaemic stroke presenting upon awakening.

Types of participants

People with acute ischaemic stroke presenting upon awakening (with neuroimaging excluding intracranial haemorrhage before randomisation). If a trial recruited both people with wake-up strokes and those whose strokes occurred while awake, we contacted the trial authors to request data for only those participants with wake-up strokes.

Types of interventions

We included all types of thrombolytic drugs, given in any dose by intravenous route: urokinase, recombinant pro-urokinase, streptokinase, and tissue plasminogen activator including alteplase, duteplase, lumbrokinase, tenecteplase, and desmoteplase.

We included all types of intra-arterial treatments: administration of thrombolytic drugs through intra-arterial catheters, mechanical

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thrombus disruption using a microcatheter or guidewires or both, angioplasty, and the use of endovascular devices.

The comparison therapy was standard medical care or placebo.

Types of outcome measures

Primary outcomes

Functional outcome at the end of the follow-up period. We defined favourable functional outcome as a modified Rankin scale (mRS) score of 0 to 2. If the mRS score was not reported, we used the trial's definition of functional outcome.

Secondary outcomes

- Death from all causes within seven to 14 days and at the end of follow-up
- Symptomatic intracranial haemorrhage within seven to 14 days
- Quality of life at the end of follow-up
- Neurological status at seven to 14 days and at the end of follow-up

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We searched for trials in all languages and arranged for the translation of relevant articles when necessary.

Electronic searches

We searched the Cochrane Stroke Group Trials Register (last searched on 9 January 2018) and the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 11) in the Cochrane Library (4 December 2017) (Appendix 1)
- MEDLINE Ovid (from 1948 to 7 December 2017) (Appendix 2)
- Embase Ovid (from 1980 to 7 December 2017) (Appendix 3)

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Information Specialist.

We searched the following trial registries for ongoing studies.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 7 December 2017) (Appendix 4)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch; searched 7 December 2017) (Appendix 5)
- ISRCTN registry (www.isrctn.com; searched 7 December 2017) (Appendix 6)
- Stroke Trials Registry, the Internet Stroke Centre; (www.strokecenter.org/trials/; searched 7 December 2017) (Appendix 7)

Searching other resources

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

- screened reference lists of relevant trials;
- contacted principal investigators of identified trials (we received replies from Masatoshi Koga and Christian Gerloff);
- used the Science Citation Index Cited Reference search for forward tracking of relevant references;
- contacted manufacturers of relevant devices and equipment (we received a reply from Penumbra Inc.).

Data collection and analysis

Selection of studies

Two review authors (MBR and HL) independently screened titles and abstracts of references obtained as a result of the searches and excluded obviously irrelevant reports. We retrieved the full-text articles for the remaining references, and two review authors (HL and EBM) independently screened the full-text articles and identified studies for inclusion, and identified and recorded reasons for exclusion of ineligible studies. Any disagreements were resolved through discussion or by consulting a third review author (EB) when necessary. We collated multiple reports of the same study so that each study, rather than each reference, was the unit of interest in the review. We recorded the selection process and completed a PRISMA flow diagram.

Data extraction and management

Two review authors (MBR and HL) independently extracted data from the report of each eligible trial onto a specially designed data extraction form. The review authors were not blinded to journal or institution.

We extracted the following data from each report.

- Method of randomisation
- Allocation concealment
- Blinding of participants, personnel, and outcome assessment
- Whether data were reported completely
- Whether data were reported selectively
- Other bias

We extracted the numbers of participants in the intervention and control groups who:

- were independent (mRS score 0 to 2) at end of follow-up: if possible, we also extracted the number of participants in each mRS category;
- died within the first seven to 14 days;
- died at the end of follow-up;
- developed symptomatic intracranial haemorrhage within the first seven to 14 days after stroke.

One review author (HL) entered the data into Review Manager 5 (RevMan 2014). Another review author (MBR) checked these data against the hard-copy data extraction forms to correct any clerical data entry errors. If any relevant data were missing from the available publications, we made direct contact with the relevant principal investigators.

Assessment of risk of bias in included studies

Two review authors (MBR and HL) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

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Any disagreements were resolved by discussion or by involving another review author (EB). We assessed the risk of bias according to the following domains.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other bias

We graded the risk of bias for each domain as high, low, or unclear and provided information from the study report together with a justification for our judgement in the 'Risk of bias' tables.

Measures of treatment effect

For dichotomous outcomes, we intended to calculate a weighted estimate of treatment effects across trials and to report odds ratios (ORs) with 95% confidence intervals (CIs). When continuous scales of measurement were used to assess the effects of treatment, we intended to use the mean difference (MD). For studies that used different scales for assessment of similar outcomes, we intended to report standardised mean differences (SMDs).

Unit of analysis issues

For each study, we considered whether groups of individuals were randomised together to the same intervention (cluster-randomised trial), individuals underwent more than one intervention (cross-over trial), or there were multiple observations for the same outcome.

Dealing with missing data

If the published information did not allow intention-to-treat analysis, we contacted the study authors to ask for follow-up data that were as complete as possible on all randomly assigned participants for the originally proposed period of follow-up. In this sensitivity analysis, we assumed that participants who were lost to follow-up in the treatment group had the worst outcomes and participants who were lost to follow-up in the control group had the best outcomes.

Assessment of heterogeneity

We intended to use the I^2 statistic to measure heterogeneity among the trials in each analysis. We intended to assess heterogeneity according to Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, studies were insufficient to allow this.

Assessment of reporting biases

We intended to use funnel plots to assess reporting bias.

Data synthesis

We intended to calculate a weighted estimate of the typical treatment effect across trials by means of a random-effects model.

When more studies are available for inclusion in the review, we will use the GRADE approach to assess the quality of the body of evidence as described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will use GRADEpro GDT to complete the Summary of findings for the main comparison (GRADEpro GDT 2015).

Subgroup analysis and investigation of heterogeneity

We intended to perform separate analyses in the following subgroups.

- Participants characterised by specific imaging criteria (e.g. findings of ischaemic penumbra)
- Participants treated at different time intervals (e.g. within three hours after awakening or longer than three hours after awakening)

Sensitivity analysis

We intended to perform a sensitivity analysis to test whether results differed when we excluded trials with high risk of bias.

RESULTS

Description of studies

Results of the search

The searches yielded 1481 references. We excluded 248 duplicates that were not relevant to the review objective. We assessed a total of 1233 records and excluded 1231 records because the abstract showed that they were not randomised trials of wake-up stroke.

We assessed two records in full. We included one study (one record). We excluded one study (one record) because it included both non-wake-up strokes and wake-up strokes, and we were unable to obtain the data from the trial authors for the portion of participants with wake-up stroke in the trial. The PRISMA flow diagram is given in Figure 1.

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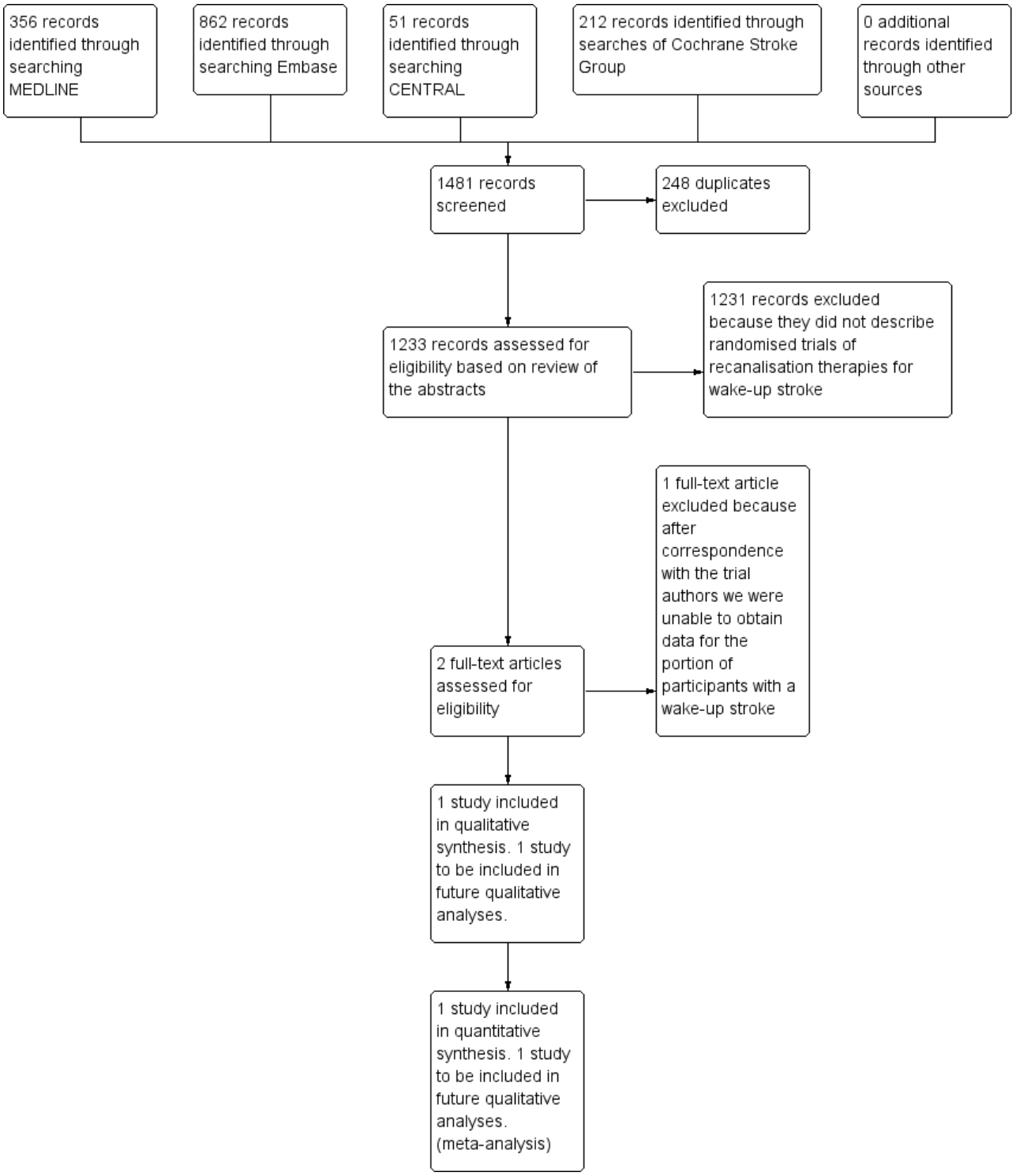
Figure 1. PRISMA flow diagram.



Included studies

We included one study that recruited people with wake-up strokes and people with strokes that occurred whilst the individual was awake (Michel 2012). This pilot trial randomised people with an unknown onset of stroke and signs on perfusion computed tomography (CT) of ischaemic tissue at risk of infarction. The trial was managed from Switzerland. The principal investigator provided data on the nine participants included in the trial. Four participants were randomised to intravenous thrombolytic therapy with alteplase (0.9 mg/kg), and five participants were randomised to placebo.

We identified six ongoing trials (NCT01455935; NCT01525290; NCT01580839; NCT01852201; NCT02002325; NCT03181360).

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Excluded studies

We excluded one study that recruited both people with wake-up strokes and people with strokes that occurred whilst the individual was awake (NCT02142283). Participants were randomised to intra-arterial treatment or control. The trial was ended after interim analyses showed effect of intra-arterial treatment. We contacted the trial authors, but they did not wish to share data until their secondary papers are published.

Risk of bias in included studies

See Figure 2. The quality of randomisation and blinding in the included study was adequate (Michel 2012). No participants were lost to follow-up. The study reported intention-to-treat analyses. This was a pilot trial and had limited statistical power.

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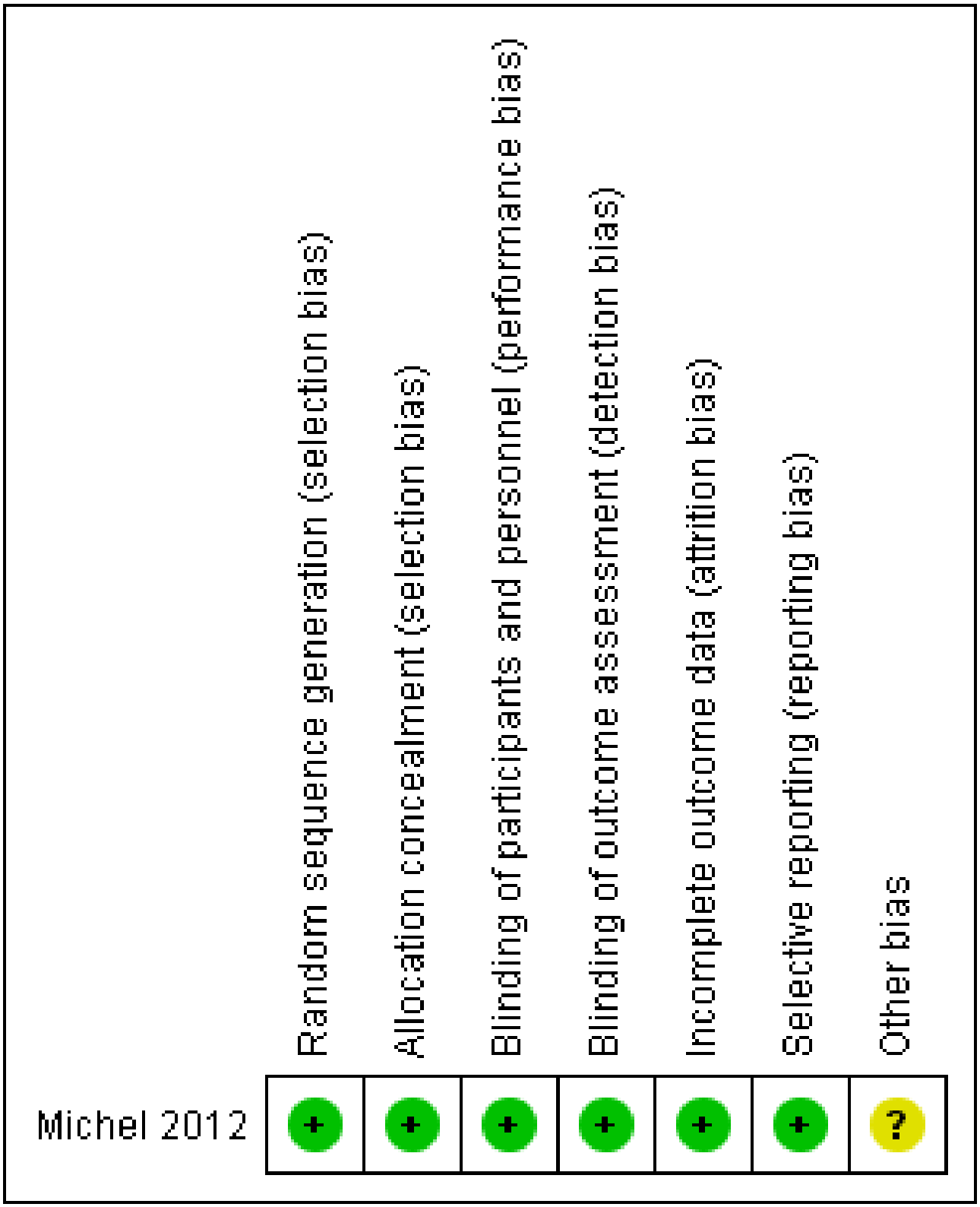
Figure 2. Risk of bias summary: judgements about each risk of bias item for the included study.



Allocation

Enrolment of participants and allocation was performed by a blinded physician. We assessed the risk of bias to be low.

Blinding

The trial was placebo controlled and employed blinded outcome assessment. We assessed the risk of bias to be low.

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Incomplete outcome data

There was no loss to follow-up. We assessed the risk of bias to be low.

Selective reporting

There was no selective reporting. We assessed the risk of bias to be low.

Other potential sources of bias

We identified no other potential sources of bias. We assessed the risk of bias to be unclear.

Effects of interventions

See: **Summary of findings for the main comparison** Recanalisation therapies compared to no recanalisation therapies for wake-up stroke

Good functional outcome (mRS 0 to 2) at the end of follow-up was observed in four of four participants in the intervention group and two of five participants in the control group. No participants were dead at the end of follow-up. No participants had symptomatic intracranial haemorrhage within the first two weeks. There were no results for quality of life at the end of follow-up or for neurological status at the end of follow-up.

We considered the sample size to be inadequate for statistical analyses.

DISCUSSION

There are six ongoing randomised controlled trials of wake-up stroke (NCT01455935; NCT01525290; NCT01580839; NCT01852201; NCT02002325; NCT03181360). One trial was recently stopped after interim analyses showed effect of intra-arterial treatment (NCT02142283). This study supports the role of intra-arterial treatment in carefully selected people with wake-up stroke. However, the findings should be interpreted with caution with respect to people that do not fulfil the inclusion criteria of that study. NCT02142283 included participants with evidence of occlusion of the intracranial internal carotid artery or the proximal middle cerebral artery that had mismatch between the severity of the clinical deficit and infarct volume on diffusion-weighted magnetic resonance imaging (MRI). Furthermore, a large proportion of the participants (> 40%) in NCT02142283 had late presenting stroke and not wake-up stroke. We excluded this trial from the review because we could not obtain extracted data on the portion of participants who had wake-up stroke.

Four trials are testing alteplase versus placebo or control (NCT01455935; NCT01525290; NCT01580839; NCT02002325). One trial is testing tenecteplase (NCT03181360), and two trials are testing the effect of intra-arterial interventions for wake-up strokes (NCT01852201; NCT02142283).

The time window for recanalisation therapies in people with wake-up stroke is unknown. NCT01455935, NCT01525290, NCT02002325, and NCT03181360 allow thrombolytic treatment to be started within 4.5 hours of symptom recognition (e.g. awaking). NCT01580839 allows thrombolytic treatment to be started nine hours from the midpoint between sleep onset or last known to be normal and time of waking. NCT02142283 includes participants between six and 24 hours after last seen well. NCT01852201 includes participants between six and 12 hours after last seen well.

The benefit of advanced imaging modalities in selecting people to treatment is unknown, as demonstrated in the MR RESCUE trial, which did not find a benefit of penumbra imaging in selecting people with stroke to intra-arterial interventions (Kidwell 2013). Six of the seven ongoing randomised controlled trials on wake-up stroke use advanced imaging modalities such as magnetic resonance imaging diffusion weighted imaging/fluid attenuated inversion recovery (MRI DWI/FLAIR) mismatch or CT/MRI penumbral mismatch for selection of participants. NCT01525290, NCT01580839, and NCT02002325 use MRI DWI/FLAIR indicating that the patient has an ischaemic lesion within the time window of thrombolytic treatment, whilst NCT01455935 and NCT01580839 use penumbra-based imaging visualising a salvageable penumbral area around the infarct core. However, the interobserver agreement for MRI DWI/FLAIR mismatch is moderate, and the sensitivity and negative predictive value is low to moderate (Thomalla 2011). Even if it is possible to include patients based on MRI DWI/FLAIR mismatch, a substantial proportion of patients that may benefit from recanalisation therapies will be excluded based on mismatch imaging.

Summary of main results

Recanalisation therapies show promise in the treatment of wake-up stroke.

The American Stroke Association recommends that thrombolytic treatment for wake-up stroke with time last known to be well at more than 4.5 hours shall not be given outside clinical trials (Demaerschalk 2016), as more evidence is needed from randomised controlled trials on the risk and benefit of recanalisation therapies for wake-up stroke.

Overall completeness and applicability of evidence

Evidence was limited to one small-sampled trial. Based on the current evidence, it is not possible to conclude whether recanalisation therapies can be recommended for wake-up stroke.

Quality of the evidence

Quality of evidence was not applicable, as the data were insufficient for statistical analysis.

Potential biases in the review process

We have not included trials that were not published on the date we carried out our searches.

Agreements and disagreements with other studies or reviews

A brief literature search did not identify other reviews on this topic. Evidence of the benefit of recanalisation therapies for wake-up stroke is limited to comparison with historical controls. These studies suggest that intravenous thrombolytic drugs and intra-arterial treatments are safe to use and may improve outcome in people with wake-up stroke (Barreto 2009; Manawadu 2013; Meretoja 2010).

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AUTHORS' CONCLUSIONS

Implications for practice

There is too little evidence from randomised controlled trials to support the routine use of recanalisation therapies in people with wake-up stroke outside of clinical trials.

Implications for research

Evidence from randomised controlled trials is highly warranted in order to evaluate the benefit of recanalisation therapies in wake-up stroke. Six trials are ongoing and may contribute to this review when completed.

ACKNOWLEDGEMENTS

We thank Brenda Thomas from the Cochrane Stroke Group for developing the search strategies used in the review and for performing the searches. We also thank Dr Patrik Michel, University of Lausanne, for contributing unpublished data from Michel 2012 to this review.

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CHARACTERISTICS OF STUDIES

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

Michel 2012

Methods	Randomised, double-blinded, placebo-controlled pilot trial
Participants	12 participants with a supratentorial stroke of unknown onset in the middle cerebral artery territory and significant volume of at-risk tissue on perfusion computed tomography. 9 of the participants had wake-up stroke, and 3 had a non-wake-up stroke of unknown onset. The study authors contributed unpublished data on the 9 participants with wake-up stroke.
Interventions	• Intravenous tissue plasminogen activator (alteplase) 0.9 mg/kg body weight up to a maximum of 90 mg, 10% as bolus, 90% over 1 hour as infusion • Matching placebo
Outcomes	Primary outcome: feasibility of study Secondary outcome: mRS 0 to 2 at 90 days' follow-up
Notes	Principal Investigator: Patrik Michel, University of Lausanne, Lausanne, Switzerland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table generated by independent pharmacist
Allocation concealment (selection bias)	Low risk	Enrolment of participants and allocation performed by blinded physician.
Blinding of participants and personnel (performance bias)	Low risk	Placebo controlled

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Michel 2012 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	No selective reporting
Other bias	Unclear risk	None found.

mRS: modified Rankin Scale

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

Study	Reason for exclusion
NCT02142283	We were unable to obtain the portion of data for the wake-up stroke participants (approximately 60%). We contacted the trial authors, but they did not wish to share data until their secondary papers are published.

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

NCT01455935

Trial name or title	WAke up Symptomatic Stroke in Acute Brain Ischemia (WASSABI) trial
Methods	Randomised, single-blinded, controlled trial
Participants	90 participants Inclusion criteria • Age: 18 to 80 years old • Ischaemic wake-up stroke (unknown time of onset but < 24 hours since last seen normal) • NIHSS 8 to 22 • Evidence of penumbra on CT perfusion as mentioned above • ASPECTS 7 or more • Signed informed consent Exclusion criteria • Evidence of intracranial haemorrhage (intracerebral haematoma, intraventricular haemorrhage, subarachnoid haemorrhage, epidural haemorrhage, acute or chronic subdural haematoma) on the baseline CT • Historical mRS of ≥ 2 • NIHSS < 8 at the time of treatment • Positive pregnancy test in women at age of childbearing • Intracranial or intraspinal surgery within 3 months • Stroke or serious head injury within 3 months

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NCT01455935 *(Continued)*

	• History of intracranial haemorrhage • Uncontrolled hypertension at time of treatment (e.g. > 185 mmHg systolic or > 110 mmHg diastolic) • Seizure at the onset of stroke • Active internal bleeding • Intracranial neoplasm • Arteriovenous malformation or aneurysm • Clinical presentation suggesting post-myocardial infarction pericarditis • Known bleeding diathesis including but not limited to current use of oral anticoagulants producing an INR > 1.7 • INR > 1.7 • Administration of heparin within 48 hours preceding the onset of stroke with an elevated aPTT at presentation • Platelet count < 100,000/mm^3 • Major surgery within 2 weeks • Gastrointestinal or urinary tract haemorrhage within 3 weeks • Aggressive treatment required to lower blood pressure • Glucose level < 50 or > 400 mg/dL • Arterial puncture at a non-compressible site or lumbar puncture within 1 week
Interventions	• Best medical care • Intravenous tissue plasminogen activator (alteplase) 0.9 mg/kg body weight up to a maximum of 90 mg, 10% as bolus, 90% over 1 hour as infusion • Intra-arterial therapy (choice of intra-arterial therapy by endovascular surgeon)
Outcomes	mRS at 90 days' follow-up
Starting date	November 2011
Contact information	Principal Investigator: Tareq Kass-Hout, Jacobs Neurological Institute, University at Buffalo Neurosurgery, USA E-mail: kasshouttareq@gmail.com
Notes	ClinicalTrials.gov identifier: NCT01455935

NCT01525290

Trial name or title	Efficacy and safety of magnetic resonance imaging-based thrombolysis in wake-up stroke (WAKE-UP)
Methods	Randomised, double-blinded, placebo-controlled trial
Participants	800 participants Clinical inclusion criteria • Clinical diagnosis of acute ischaemic stroke with unknown symptom onset (e.g. stroke symptoms recognised on awakening) • Last known well (without neurological symptoms) > 4.5 hours of treatment initiation • Measurable disabling neurological deficit (defined as an impairment of 1 or more of the following: language, motor function, cognition, gaze, vision, neglect) • Age 18 to 80 years • Treatment can be started within 4.5 hours of symptom recognition (e.g. awakening)

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NCT01525290 *(Continued)*

- Written informed consent by patient or proxy

Imaging inclusion criteria

- Acute stroke MRI including DWI and FLAIR completed
- MRI showing a pattern of "diffusion weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) -mismatch," i.e. acute ischaemic lesion visibly on DWI ("positive DWI") but no marked parenchymal hyperintensity visible on FLAIR ("negative FLAIR") indicative of an acute ischaemic lesion ≤ 4.5 hours of age

Clinical exclusion criteria

- Planned or anticipated treatment with endovascular reperfusion strategies (e.g. intra-arterial thrombolysis, mechanical recanalisation techniques)
- Pre-stroke disability (inability to carry out all daily activities, requiring some help or supervision, i.e. slight disability corresponding to an mRS score > 1)
- Participation in any investigational study in the previous 30 days
- Severe stroke by clinical assessment (e.g. NIHSS > 25)
- Hypersensitivity to alteplase or any of the excipients
- Pregnancy or lactating (formal testing needed in woman of childbearing potential; childbearing potential is assumed in women up to 55 years of age)
- Significant bleeding disorder at present or within past 6 months
- Known haemorrhagic diathesis
- Manifest or recent severe or dangerous bleeding
- Known history of or suspected intracranial haemorrhage
- Suspected subarachnoid haemorrhage (even if CT is negative) or condition after subarachnoid haemorrhage from aneurysm
- History of central nervous system damage (e.g. neoplasm, aneurysm, intracranial or spinal surgery)
- Recent (within 10 days) traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood vessel
- Current use of anticoagulants (e.g. phenprocoumon, warfarin, new anticoagulants such as dabigatran) or current use of heparin and elevated thromboplastin time (low-dose subcutaneous heparin is allowed)
- Platelet count < 100,000/mm^3
- Blood glucose < 50 or > 400 mg/dL (< 2.8 or 22.2 mmol/L)
- Severe uncontrolled hypertension, i.e. systolic blood pressure > 185 mmHg or diastolic blood pressure > 110 mmHg or requiring aggressive medication to maintain blood pressure within these limits (routine medical treatment is allowed to lower the blood pressure below these limits)
- Manifest or recent bacterial endocarditis, pericarditis
- Manifest or recent acute pancreatitis
- Documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial aneurysm, arterial/venous malformations
- Neoplasm with increased bleeding risk
- Manifest severe liver disease including hepatic failure, cirrhosis, portal hypertension, and active hepatitis
- Major surgery or significant trauma in past 3 months
- Stroke within 30 days
- Life expectancy 6 months or less by judgement of the investigator
- Any condition associated with a significantly increased risk of severe bleeding not mentioned above
- Any contraindication to MRI (e.g. cardiac pacemaker)

Imaging exclusion criteria

- Poor MRI quality precluding interpretation according to the study protocol
- Any sign of intracranial haemorrhage on baseline MRI

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NCT01525290 *(Continued)*

	• FLAIR showing a marked parenchymal hyperintensity in a region corresponding to the acute DWI lesion indicative of an acute ischaemic lesion with a high likelihood of being > 4.5 hours old • Large DWI lesion volume > 1/3 of the middle cerebral artery or > 50% of the anterior cerebral artery or posterior cerebral artery territory (visual inspection) or > 100 mL • Any MRI findings indicative of a high risk of symptomatic intracranial haemorrhage related to potential IV alteplase treatment in the judgement of the investigator
Interventions	• IV tissue plasminogen activator (alteplase) 0.9 mg/kg body weight up to a maximum of 90 mg, 10% as bolus, 90% over 1 hour as infusion • Matching placebo
Outcomes	• Favourable outcome (mRS 0 to 1) at 90 days' follow-up • Mortality at 90 days' follow-up • Death or dependency (mRS 4 to 6) at 90 days' follow-up
Starting date	September 2012
Contact information	Principal Investigator: Goetz Thomalla, Universitätsklinikum Hamburg-Eppendorf, Germany E-mail: thomalla@uke.uni-hamburg.de
Notes	ClinicalTrials.gov identifier: NCT01525290

NCT01580839

Trial name or title	EXtending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND)
Methods	Randomised, double-blind, placebo-controlled trial
Participants	400 participants Inclusion criteria • Participants presenting with acute ischaemic stroke • Participant, family member or legally responsible person depending on local ethics requirements has given informed consent • Participant's age is ≥ 18 years • Treatment onset can commence within ≥ 3 to 9 hours after stroke onset according to registered product information, or within 4.5 to 9 hours according to locally accepted guidelines.* (*Guidelines are currently under international review - advisory statement issued by the Stroke Council, American Heart Association, and American Stroke Association.) • Patients who awake with stroke may be included if neurological and other exclusion criteria are satisfied. These 'wake up' strokes are defined as having no symptoms at sleep onset, but stroke symptoms on waking. The time of stroke onset is to be taken as the midpoint between sleep onset (or last known to be normal) and time of waking. The maximum time window for randomisation is then 9 hours from the midpoint as described • NIHSS score of ≥ 4 to 26 with clinical signs of hemispheric infarction • Penumbral imaging - using a Tmax > 6-second delay, a perfusion (PWI) lesion volume to diffusion (DWI) lesion volume ratio > 1.2, a DWI volume ≤ 70 mL, and a perfusion lesion volume-diffusion lesion volume difference > 10 mL • Patients may be consented before or after penumbral screening depending upon local practice. The entire cohort of patients consented into the study will be followed up with clinical assessments and biomarker studies regardless of eligibility for randomisation to treatment based on penumbral mismatch criteria Exclusion criteria

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NCT01580839 *(Continued)*

	• Intracranial haemorrhage identified by CT or MRI • Rapidly improving symptoms, particularly if in the judgement of the managing clinician improvement is likely to result in the patient having an NIHSS score of < 4 at randomisation • Pre-stroke mRS score of ≥ 2 (indicating previous disability) • Contraindication to imaging with magnetic resonance with contrast agents • Infarct core > 1/3 middle cerebral artery territory qualitatively • Participation in any investigational study in the previous 30 days • Any terminal illness such that the patient would not be expected to survive more than 1 year • Any condition that could impose hazards to the patient if study therapy is initiated or affect the participation of the patient in the study (this applies to patients with severe microangiopathy such as haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura). The judgement is left to the discretion of the investigator • Pregnant women (clinically evident) • Previous stroke within last 3 months • Recent past history or clinical presentation of intracerebral haemorrhage, subarachnoid haemorrhage, arteriovenous malformation, aneurysm, or cerebral neoplasm. At the discretion of each investigator • Current use of oral anticoagulants and a prolonged prothrombin time (INR > 1.6) • Use of heparin, except for low-dose subcutaneous heparin, in the previous 48 hours and an activated prolonged partial thromboplastin time exceeding the upper limit of the local laboratory normal range • Use of glycoprotein IIb-IIIa inhibitors within the past 72 hours. Use of single or dual agent oral platelet inhibitors (clopidogrel and/or low-dose aspirin) prior to study entry is permitted • Clinically significant hypoglycaemia • Uncontrolled hypertension defined by a blood pressure > 185 mmHg systolic or > 110 mmHg diastolic on at least 2 separate occasions at least 10 minutes apart, or requiring aggressive treatment to reduce the blood pressure to within these limits. The definition of 'aggressive treatment' is left to the discretion of the responsible investigator • Hereditary or acquired haemorrhagic diathesis • Gastrointestinal or urinary bleeding within the preceding 21 days • Major surgery within the preceding 14 days that poses risk in the opinion of the investigator • Exposure to a thrombolytic agent within the previous 72 hours
Interventions	• Intravenous tissue plasminogen activator (alteplase) 0.9 mg/kg body weight up to a maximum of 90 mg, 10% as bolus, 90% over 1 hour as infusion • Matching placebo
Outcomes	mRS 0 to 1 at 90 days' follow-up
Starting date	June 2010
Contact information	Principal Investigator: Geoffrey Donnan, National Stroke Research Institute, Australia Principal Investigator: Stephen Davis, University of Melbourne, Australia Contact: Sue Bates, e-mail: sbates@neurotrialsaustralia.com
Notes	ClinicalTrials.gov identifier: NCT01580839 (Australian part) and NCT00887328 (international part)

NCT01852201

Trial name or title	PerfusiOn imaging Selection of Ischemic sTroke patIents for endoVascular thErapy (POSITIVE)
Methods	Randomised, single-blinded trial

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NCT01852201 *(Continued)*

Participants	750 participants Inclusion criteria • Age 18 and older (i.e. candidates must have had their 18th birthday) • NIHSS ≥ 8 at the time of neuroimaging • Presenting or persistent symptoms within 6 to 12 hours of when groin puncture can be obtained • Neuroimaging demonstrates large vessel proximal occlusion (distal internal carotid artery through middle cerebral artery M1 bifurcation) • The operator feels that the stroke can be appropriately treated with traditional endovascular techniques (endovascular mechanical thrombectomy without adjunctive devices such as stents) • Patients within 6 to 12 hours of symptom onset who have received intravenous alteplase without improvement in symptoms are eligible for this study. Patients presenting earlier than 6 hours should be treated according to local standard of care • Pre-event mRS score 0 to 1 • Consenting requirements met according to local institutional review board Exclusion criteria • Patient is less than 6 hours from symptom onset • Rapidly improving neurologic examination • Absence of large vessel occlusion on non-invasive imaging • Known or suspected pre-existing (chronic) large vessel occlusion in the symptomatic territory • Absence of an associated large penumbra as defined by physiologic imaging according to standard of practice at the participating institution • Any intracranial haemorrhage in the last 90 days • Known irreversible bleeding disorder • Known hereditary or acquired haemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR > 2.5 or institutionally equivalent prothrombin time of 2.5 times normal • Platelet count < 100 x 103 cells/mm^3 or known platelet dysfunction • Inability to tolerate, clinically documented evidence in medical history of adverse reaction, or contraindication to medications used in treatment of the stroke • Contraindication to CT or MRI (i.e. iodine contrast allergy or other condition that prohibits imaging from either CT or MRI) • Known allergy to contrast used in angiography that cannot be medically controlled • Relative contraindication to angiography (e.g. serum creatinine > 2.5 mg/dL) • Women who are currently pregnant or breastfeeding (women of childbearing potential must have a negative pregnancy test prior to the study procedure - either serum or urine) • Evidence of active infection (indicated by fever at or over 99.9 °F and/or open draining wound) at the time of randomisation • Current use of cocaine or other vasoactive substance • Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments through 90 days • Patients who lack the necessary mental capacity to participate or who are unwilling or unable to comply with the protocol's follow-up appointment schedule (based on the investigator's judgement) Head CT or MRI scan exclusion criteria • Presence of blood on imaging (subarachnoid haemorrhage, intracerebral haemorrhage, etc.) • High-density lesion consistent with haemorrhage of any degree • Significant mass effect with midline shift • Large (more than 1/3 of the middle cerebral artery) regions of clear hypodensity on the baseline CT scan or ASPECTS of < 7; sulcal effacement and/or loss of grey-white differentiation alone are not contraindications for treatment

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NCT01852201 *(Continued)*

Interventions	Endovascular treatment plus best medical treatment or best medical treatment alone
Outcomes	mRS score at 90 days' follow-up
Starting date	September 2013
Contact information	Adrian Parker 843-792-3164 parkerad@musc.edu
Notes	ClinicalTrials.gov identifier: NCT01852201 Not a trial of wake-up stroke per se, but the trial will include a substantial proportion of participants with wake-up stroke.

NCT02002325

Trial name or title	THrombolysis for Acute Wake-up and unclear-onset Strokes with alteplase at 0.6 mg/kg Trial (THAWS)
Methods	Randomised, single-blinded, controlled trial
Participants	300 participants Inclusion criteria • Clinical diagnosis of acute ischaemic stroke with unknown symptom onset (e.g. acute wake-up ischaemic stroke, acute ischaemic stroke with unknown time of symptom onset) • Last known well without neurological symptoms > 4.5 hours and < 12 hours of treatment initiation • Treatment can be started within 4.5 hours of symptom recognition (e.g. awaking) • Acute stroke MRI including DWI and FLAIR completed • ASPECTS on initial DWI is 5 or more • No marked parenchymal hyperintensity visible on FLAIR • Initial NIHSS ≥ 5 and ≤ 25 • Written informed consent by patient or next of kin Exclusion criteria • Pre-stroke mRS > 1 (patients who have inability to carry out all daily activities and require some help or supervision) • Contraindications in the Japanese guideline for the intravenous application of recombinant tissue-type plasminogen activator (alteplase) • History of non-traumatic intracranial haemorrhage • History of stroke within the last 1 month (excluding transient ischaemic attack) • History of significant head/spinal injury or surgery within the last 3 months • History of gastrointestinal or urinary tract bleeding within the last 21 days • History of major surgery or significant trauma other than head injury within the last 14 days • Hypersensitivity to alteplase • Suspected subarachnoid haemorrhage • Concurrent acute aortic dissection • Concurrent haemorrhage (e.g. intracranial, gastrointestinal, urinary tract, or retroperitoneal, haemoptysis) • Systolic blood pressure ≥ 185 mmHg despite antihypertensive therapy • Diastolic blood pressure ≥ 110 mmHg despite antihypertensive therapy • Significant hepatic disorder • Acute pancreatitis

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NCT02002325 *(Continued)*

	• Blood glucose < 50 mg/dL or > 400 mg/dL • Platelet count ≤ 100,000/mm^3 • International normalised ratio of prothrombin time > 1.7 or prolonged aPTT > 1.5 times the baseline value (> approximately 40 seconds only as a guide) for patients on anticoagulation therapy or those with abnormal coagulation • Any contraindication to MRI (e.g. cardiac pacemaker) • Extensive early ischaemic change in brainstem or cerebellum (e.g. more than half of brainstem or more than 1 hemisphere of cerebellum) • Planned or anticipated treatment with surgery or endovascular reperfusion strategies (e.g. intra-arterial thrombolysis, mechanical recanalisation techniques) • Pregnant, lactating, or potentially pregnant • Life expectancy 6 months or less by judgement of the investigator • Inappropriate for study enrolment by judgement of the investigator
Interventions	• Intravenous tissue plasminogen activator (alteplase) 0.6 mg/kg body weight up to a maximum of 60 mg, 10% as bolus, 90% over 1 hour as infusion • Best medical care
Outcomes	Favourable outcome (mRS score 0 to 1) at 90 days' follow-up
Starting date	April 2014
Contact information	Principal Investigator: Kazunori Toyoda, National Cerebral and Cardiovascular Center, Japan Contact person: Masatoshi Koga, koga@ncvc.go.jp
Notes	ClinicalTrials.gov identifier: NCT02002325

NCT03181360

Trial name or title	Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST)
Methods	PROBE; prospective, randomised, open, blinded-endpoint
Participants	500 participants Inclusion criteria • Stroke symptoms on awakening that were not present before sleep • Clinical diagnosis of stroke with limb weakness with an NIHSS score > 5, or dysphasia • Treatment with tenecteplase is possible within 4.5 hours of awakening • Written consent from the patient, non-written consent from the patient (witnessed by non-participating healthcare personnel), or written consent from the nearest family member Exclusion criteria • Age < 18 years • NIHSS score > 25 or NIHSS consciousness score > 2, or seizures during stroke onset • Findings on plain CT that indicate that the patient is unlikely to benefit from treatment: infarction comprising more than > 1/3 of the middle cerebral artery territory on plain CT or CT perfusion • Intracranial haemorrhage, structural brain lesions that can mimic stroke (e.g. cerebral tumour) • Patient will be treated with intra-arterial interventions for proximal cerebral artery occlusion • Active internal bleeding of high risk of bleeding, e.g. major surgery, trauma or gastrointestinal or urinary tract haemorrhage within the previous 21 days, or arterial puncture at a non-compressible site within the previous 7 days. Any known defect in coagulation, e.g. current use of vitamin K an-

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NCT03181360 *(Continued)*

	tagonist with an INR > 1.7 or prothrombin time > 15 seconds, or use of direct thrombin inhibitors or direct factor Xa inhibitors during the last 24 hours (unless reversal of effect can be achieved by agents such as idarucizumab or andexanet) or with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, ecarin clotting time, thrombin time, or appropriate factor Xa activity assays), or heparins during the last 24 hours or with an elevated aPTT greater than the upper limit of normal, known defect of clotting or platelet function or platelet count below 100,000/mm^3 (but patients on antiplatelet agents may be included), ischaemic stroke or myocardial infarction in previous 3 months, previous intracranial haemorrhage, severe traumatic brain injury, or intracranial or intraspinal operation in previous 3 months, or known intracranial neoplasm, arteriovenous malformation, or aneurysm • Contraindications to tenecteplase, e.g. acute bacterial endocarditis or pericarditis; acute pancreatitis; severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension; active hepatitis; systemic cancer with increased bleeding risk; haemostatic defect including secondary to severe hepatic, renal disease; organ biopsy; prolonged cardiopulmonary resuscitation > 2 min (within 2 weeks) • Persistent blood pressure elevation (systolic ≥ 185 mmHg or diastolic ≥ 110 mmHg), despite blood pressure-lowering treatment • Blood glucose < 2.7 or > 20.0 mmol/L (use of finger-stick measurement devices is acceptable) • Pregnancy, positive pregnancy test, childbirth during last 10 days, or breastfeeding. In any woman of childbearing potential, a pregnancy test must be performed and the result assessed before trial entry • Other serious or life-threatening disease before the stroke: severe mental or physical disability (e.g. Mini Mental Status score < 20 or mRS score ≥ 3), or life expectancy less than 12 months • Patient unavailable for follow-up (e.g. no fixed address)
Interventions	• Tenecteplase + best standard treatment or no tenecteplase + best standard treatment • Tenecteplase is given as a single-dose intravenous injection of recombinant fibrin-specific tissue plasminogen activator (tenecteplase) 0.25 mg (200 IU) per kg body weight up to a maximum of 25 mg (5000 IU), administered as a bolus over approximately 10 seconds
Outcomes	Primary outcome measures • Functional outcome at 3 months. Functional outcome will be assessed by the mRS, values 0 to 6 Secondary outcome measures • Symptomatic intracranial haemorrhage during the first 7 days. Symptoms (neurological deterioration, new headache, new acute hypertension, new nausea or vomiting, or sudden decrease in conscious level). Intracranial haemorrhage on brain MRI or CT. Asymptomatic intracranial haemorrhage during the first 7 days. Intracranial haemorrhage on brain MRI or CT without: neurological deterioration, new headache, new acute hypertension, new nausea or vomiting, or sudden decrease in consciousness level • Recurrent ischaemic stroke during the first 7 days. Neurological deterioration (increase of ≥ 2 on the NIHSS, after exclusion of other causes for neurological deterioration) occurring after 72 hours will be considered as a recurrent stroke. A recurrent stroke will be classified as ischaemic if imaging has excluded haemorrhage • Death from all causes (time frame: first 7 days). Death will be classified according to cause: initial stroke, recurrent stroke, myocardial infarction, pneumonia, or other • Death from all causes (time frame: 3 months). Death will be classified according to cause: initial stroke, recurrent stroke, myocardial infarction, pneumonia, or other • Barthel Index score (time frame: 3 months). Ordinal scale for measuring performance in activities of daily living • EuroQol Score (EQ-5D) (time frame: 3 months). Measure of health-related quality of life • Mini Mental State Examination (time frame: 3 months). 30-point questionnaire for measurement of cognitive impairment • Health-economic variables. Costs related to length of hospital stay, nursing home care after discharge, rehospitalisations during first 3 months

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NCT03181360 *(Continued)*	• Functional outcome at 3 months. Functional outcome assessed by dichotomised mRS score; values 0 to 1 vs 2 to 6
Starting date	June 2017
Contact information	Trial Manager: Melinda B Roaldsen; e-mail: melinda.b.roaldsen@uit.no or twist@uit.no
Notes	ClinicalTrials.gov identifier NCT03181360

aPTT: activated partial thromboplastin time
ASPECTS: Alberta Stroke Program Early CT score
CT: computed tomography
DWI: diffusion-weighted imaging
FLAIR: fluid attenuated inversion recovery
INR: international normalised ratio
IV: intravenous
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
PWI: perfusion-weighted imaging

APPENDICES

Appendix 1. CENTRAL search strategy

#1[mh ^"cerebrovascular disorders"] or [mh ^"basal ganglia cerebrovascular disease"] or [mh ^"brain ischemia"] or [mh "brain infarction"] or [mh ^"hypoxia-ischemia, brain"] or [mh ^"carotid artery diseases"] or [mh ^"carotid artery thrombosis"] or [mh ^"carotid artery, internal, dissection"] or [mh ^"intracranial arterial diseases"] or [mh "cerebral arterial diseases"] or [mh ^"infarction, anterior cerebral artery"] or [mh ^"infarction, middle cerebral artery"] or [mh ^"infarction, posterior cerebral artery"] or [mh "intracranial embolism and thrombosis"] or [mh stroke] or [mh ^"vertebral artery dissection"]
#2isch*emi* near/6 (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva or attack*):ti,ab
#3(brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or mca* or "anterior circulation") near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*):ti,ab
#4#1 or #2 or #3
#5[mh ^wakefulness] or [mh ^sleep]
#6("wake up" or "wake-up" or "wakes up" or "wakes-up"):ti,ab
#7(waking* or awake* or awoke):ti,ab
#8(during near/5 sleep*):ti,ab
#9(whil* near/5 (sleep* or asleep)):ti,ab
#10((unknown or unclear or uncertain or indefinite or "not known") near/10 onset):ti,ab
#11#5 or #6 or #7 or #8 or #9 or #10
#12[mh ^"thrombolytic therapy"]
#13[mh ^"fibrinolytic agents"] or [mh ^plasmin] or [mh ^plasminogen] or [mh ^"tissue plasminogen activator"] or [mh "plasminogen activators"] or [mh ^"urokinase-type plasminogen activator"] or [mh streptokinase]
#14[mh ^fibrinolysis]
#15(thromboly* or fibrinoly* or recanalis* or recanaliz*):ti,ab
#16((clot* or thrombus) near/5 (lyse or lysis or dissolve* or dissolution or bust*)):ti,ab
#17(tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse):ti,ab
#18(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 or tenecteplase or desmoteplase or amediplase or monteplase or nasaruplase or silteplase):ti,ab
#19[mh ^"radiography, interventional"] or [mh ^"radiology, interventional"]
#20[mh ^catheterization] or [mh ^angioplasty] or [mh ^"angioplasty, balloon"] or [mh ^"angioplasty, balloon, laser-assisted"] or [mh ^"angioplasty, laser"] or [mh ^atherectomy] or [mh ^"balloon dilatation"] or [mh ^"catheter ablation"]
#21[mh ^Stents]
#22[mh ^"mechanical thrombolysis"] or [mh ^thrombectomy] or [mh ^embolectomy]
#23[mh ^"blood vessel prosthesis"] or [mh ^"blood vessel prosthesis implantation"]
#24[mh ^"Cerebral Revascularization"] or [mh ^reperfusion] or [mh ^dilatation]

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#25(interventional near/3 (radiolog* or radiograph* or neuroradiolog*)):ti,ab
#26(angioplast* or stent*):ti,ab
#27(thrombectomy or embolectomy or atherect*):ti,ab
#28(thromboaspiration or arterial next recanali*ation):ti,ab
#29((mechanical or radiolog* or pharmacomechanical or laser or endovascular or neurovascular) near/5 (thrombolys* or reperfusion or fragment* or aspiration or recanali*ation or clot next lys*)):ti,ab
#30((clot or thrombus or thrombi or embol*) near/5 (aspirat* or remov* or retriev* or fragment* or retract* or extract* or obliterat* or dispers* or disrupt* or disintegrate*)):ti,ab
#31((retrieval or extraction) near/5 device*):ti,ab
#32(endoluminal next repair*):ti,ab
#33(blood vessel near/5 (prosthesis or implantat*)):ti,ab
#34((merci or concentric) next retriever):ti,ab
#35(endovascular next snare* or neuronet or microsnare or "X-ciser" or angiojet):ti,ab
#36[mh ^ultrasonics] or [mh ^"ultrasonic therapy"] or [mh ^ultrasonography] or [mh "ultrasonography, Doppler"] or [mh ^"ultrasonography, interventional"]
#37(ultrasound* or ultrasonic* or ultrasonogra* or sonograph* or insonation):ti,ab
#38((transcranial near/5 doppler) or TCD or TCCD):ti,ab
#39[mh /US]
#40(sonothrombolysis or sonothromboly* or sonolys* or sonothrombotripsy or thrombotripsy):ti,ab
#41{or #12-#40}
#42#4 and #11 and #41

Appendix 2. MEDLINE search strategy

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or brain ischemia/ or exp brain infarction/ or hypoxia-ischemia, brain/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid artery, internal, dissection/ or intracranial arterial diseases/ or cerebral arterial diseases/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or exp "intracranial embolism and thrombosis"/ or exp stroke/ or vertebral artery dissection/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. 1 or 2 or 3
5. wakefulness/ or sleep/
6. (wake up or wake-up or wakes up or wakes-up).tw.
7. (waking$ or awake$ or awoke).tw.
8. (during adj5 sleep$).tw.
9. (whil$ adj5 (sleep$ or asleep)).tw.
10. ((unknown or unclear or uncertain or indefinite or "not known") adj10 onset).tw.
11. 5 or 6 or 7 or 8 or 9 or 10
12. thrombolytic therapy/
13. fibrinolytic agents/ or fibrinolysin/ or plasminogen/ or tissue plasminogen activator/ or exp plasminogen activators/ or urokinase-type plasminogen activator/ or exp streptokinase/
14. fibrinolysis/
15. (thromboly$ or fibrinoly$ or recanalis$ or recanaliz$).tw.
16. ((clot$ or thrombus) adj5 (lyse or lysis or dissolve$ or dissolution or bust$)).tw.
17. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
18. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).nm.
19. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or amediplase or monteplase or nasaruplase or silteplase).tw.
20. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or amediplase or monteplase or nasaruplase or silteplase).nm.
21. radiography, interventional/ or radiology, interventional/
22. catheterization/ or angioplasty/ or angioplasty, balloon/ or angioplasty, balloon, laser-assisted/ or angioplasty, laser/ or atherectomy/ or balloon dilatation/ or catheter ablation/
23. Stents/
24. mechanical thrombolysis/ or thrombectomy/ or embolectomy/
25. blood vessel prosthesis/ or blood vessel prosthesis implantation/
26. Cerebral Revascularization/ or reperfusion/ or dilatation/
27. (interventional adj3 (radiolog$ or radiograph$ or neuroradiolog$)).tw.
28. (angioplast$ or stent$).tw.

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29. (thrombectomy or embolectomy or atherect$).tw.
30. (thromboaspiration or arterial recanali?ation).tw.
31. ((mechanical or radiolog$ or pharmacomechanical or laser or endovascular or neurovascular) adj5 (thrombolys$ or reperfusion or fragmentation or aspiration or recanali?ation or clot lys$)).tw.
32. ((clot or thrombus or thrombi or embol$) adj5 (aspirat$ or remov$ or retriev$ or fragment$ or retract$ or extract$ or obliterat$ or dispers$ or disrupt$ or disintegrate$)).tw.
33. ((retrieval or extraction) adj5 device$).tw.
34. endoluminal repair$.tw.
35. (blood vessel adj5 (prosthesis or implantat$)).tw.
36. ((merci or concentric) adj retriever).tw.
37. (endovascular snare$ or neuronet or microsnare or X-ciser or angiojet).tw.
38. ultrasonics/ or ultrasonic therapy/ or ultrasonography/ or exp ultrasonography, doppler/ or ultrasonography, interventional/
39. (ultrasound$ or ultrasonic$ or ultrasonogra$ or sonograph$ or insonation).tw.
40. ((transcranial adj5 doppler) or TCD or TCCD).tw.
41. ultrasonography.fs.
42. (sonothrombolysis or sonothromboly$ or sonolys$ or sonothrombotripsy or thrombotripsy).tw.
43. or/12-42
44. 4 and 11 and 43
45. exp animals/ not humans.sh.
46. 44 not 45

Appendix 3. Embase search strategy

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or lacunar stroke/ or cardioembolic stroke/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/ or stroke patient/ or stroke unit/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. 1 or 2 or 3
5. wakefulness/ or sleep/
6. (wake up or wake-up or wakes up or wakes-up).tw.
7. (waking$ or awake$ or awoke).tw.
8. (during adj5 sleep$).tw.
9. (whil$ adj5 (sleep$ or asleep)).tw.
10. ((unknown or unclear or uncertain or indefinite or "not known") adj10 onset).tw.
11. 5 or 6 or 7 or 8 or 9 or 10
12. fibrinolytic therapy/
13. fibrinolytic agent/ or plasmin/ or plasminogen/ or exp plasminogen activator/
14. blood clot lysis/
15. fibrinolysis/
16. (thromboly$ or fibrinoly$ or recanalis$ or recanaliz$).tw.
17. ((clot$ or thrombus) adj5 (lyse or lysis or dissolve$ or dissolution or bust$)).tw.
18. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
19. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or amediplase or monteplase or nasaruplase or silteplase).tw.
20. interventional radiology/ or endovascular surgery/
21. percutaneous transluminal angioplasty/ or angioplasty/ or laser angioplasty/ or catheterization/ or catheter ablation/ or balloon dilatation/ or exp atherectomy/
22. stent/
23. thrombectomy/ or exp percutaneous thrombectomy/ or embolectomy/
24. artery prosthesis/
25. cerebral revascularization/ or reperfusion/ or artery dilatation/ or recanalization/
26. (interventional adj3 (radiolog$ or radiograph$ or neuroradiolog$)).tw.
27. (angioplast$ or stent$).tw.
28. (thrombectomy or embolectomy or atherect$).tw.
29. (thromboaspiration or arterial recanali?ation).tw.
30. ((mechanical or radiolog$ or pharmacomechanical or laser or endovascular or neurovascular) adj5 (thrombolys$ or reperfusion or fragment$ or aspiration or recanali?ation or clot lys$)).tw.
31. ((clot or thrombus or thrombi or embol$) adj5 (aspirat$ or remov$ or retriev$ or fragment$ or retract$ or extract$ or obliterat$ or dispers$ or disrupt or disintegrate$)).tw.

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32. ((retrieval or extraction) adj5 device$).tw.
33. endoluminal repair$.tw.
34. ((blood vessel or artery) adj5 (prosthesis or implantat$)).tw.
35. ((merci or concentric) adj retriever).tw.
36. (endovascular snare$ or neuronet or microsnare or X-ciser or angiojet).tw.
37. ultrasound/ or exp ultrasound therapy/ or echography/ or doppler echography/ or intravascular ultrasound/
38. (ultrasound$ or ultrasonic$ or ultrasonogra$ or sonograph$ or insonation).tw.
39. ((transcranial adj5 doppler) or TCD or TCCD).tw.
40. (sonothrombolysis or sonothromboly$ or sonolys$ or sonothrombotripsy or thrombotripsy).tw.
41. or/12-40
42. 4 and 11 and 41
43. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
44. 42 not 43

Appendix 4. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov search strategy

Advanced search:
Recruitment status: All studies
Condition: Stroke
Other terms: awakening OR wake-up

Appendix 5. WHO International Clinical Trials Registry Platform search strategy

Advanced search:
Recruitment Status: ALL
Condition: Stroke
Other terms: awakening OR wake-up

Appendix 6. ISRCTN Registry search strategy

Advanced search:
Text search: (awakening OR "wake-up") AND stroke

Appendix 7. Stroke Trials Registry search strategy

Keywords: wake

CONTRIBUTIONS OF AUTHORS

MBR: data collection, drafting of the protocol.
HL: conception and design of the review, data collection, drafting of the protocol.
EBM and EB: conception and design of the review, commenting on protocol drafts.

DECLARATIONS OF INTEREST

MBR: none known
HL: none known
EBM: none known
EB: none known

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- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no differences between protocol and review.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Sleep; *Wakefulness; Feasibility Studies; Fibrinolytic Agents [*therapeutic use]; Mechanical Thrombolysis; Pilot Projects; Randomized Controlled Trials as Topic; Stroke [drug therapy] [*etiology]; Time Factors; Tissue Plasminogen Activator [*therapeutic use]

MeSH check words

Humans

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