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Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic wake-up stroke (Review)

Roaldsen MB, Lindekleiv H, Mathiesen EB

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[Intervention Review]

Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic 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 previously been considered to be ineligible for thrombolytic treatment because the time of stroke onset is unknown. However, recent studies suggest benefit from recanalisation therapies in selected patients.

Objectives

To assess the effects of intravenous thrombolysis and endovascular thrombectomy versus control in people with acute ischaemic stroke presenting on awakening from sleep.

Search methods

We searched the Cochrane Stroke Group Trials Register (last search 24 of May 2021). In addition, we searched the following electronic databases in May 2021: Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 4 of 12, April 2021) in the Cochrane Library, MEDLINE, Embase, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform. We searched the Stroke Trials Registry (last search 7 December 2017, as the site is currently inactive). We also screened references lists of relevant trials, contacted trialists, and undertook forward tracking of relevant references.

Selection criteria

Randomised controlled trials (RCTs) of intravenous thrombolytic drugs or endovascular thrombectomy treatments in people with acute ischaemic stroke presenting upon awakening.

Data collection and analysis

Two review authors applied the inclusion criteria, extracted data, and assessed risk of bias and the certainty of the evidence using the GRADE approach. We obtained both published and unpublished data for participants with wake-up strokes. We excluded participants with strokes of unknown onset if the symptoms did not begin upon awakening.

Main results

We included seven trials with a total of 980 participants, of which five trials with 775 participants investigated intravenous thrombolytic treatment and two trials with 205 participants investigated endovascular thrombectomy in large vessel occlusion in the anterior intracranial circulation. All trials used advanced imaging for selecting patients to treat.

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For intravenous thrombolytic treatment, good functional outcome (defined as modified Rankin Scale score 0 to 2) at 90 days follow-up was observed in 66% of participants randomised to thrombolytic treatment and 58% of participants randomised to control (risk ratio (RR) 1.13, 95% confidence interval (CI) 1.01 to 1.26; P = 0.03; 763 participants, 5 RCTs; high-certainty evidence). Seven per cent of participants randomised to intravenous thrombolytic treatment and 10% of participants randomised to control had died at 90 days follow-up (RR 0.68, 95% CI 0.43 to 1.07; P = 0.09; 763 participants, 5 RCTs; high-certainty evidence). Symptomatic intracranial haemorrhage occurred in 3% of participants randomised to intravenous thrombolytic treatment and 1% of participants randomised to control (RR 3.47, 95% CI 0.98 to 12.26; P = 0.05; 754 participants, 4 RCTs; high-certainty evidence).

For endovascular thrombectomy of large vessel occlusion, good functional outcome at 90 days follow-up was observed in 46% of participants randomised to endovascular thrombectomy and 9% of participants randomised to control (RR 5.12, 95% CI 2.57 to 10.17; P < 0.001; 205 participants, 2 RCTs; high-certainty evidence). Twenty-two per cent of participants randomised to endovascular thrombectomy and 33% of participants randomised to control had died at 90 days follow-up (RR 0.68, 95% CI 0.43 to 1.07; P = 0.10; 205 participants, 2 RCTs; high-certainty evidence).

Authors' conclusions

In selected patients with acute ischaemic wake-up stroke, both intravenous thrombolytic treatment and endovascular thrombectomy of large vessel occlusion improved functional outcome without increasing the risk of death. However, a possible increased risk of symptomatic intracranial haemorrhage associated with thrombolytic treatment cannot be ruled out. The criteria used for selecting patients to treatment differed between the trials. All studies were relatively small, and six of the seven studies were terminated early. More studies are warranted in order to determine the optimal criteria for selecting patients for treatment.

PLAIN LANGUAGE SUMMARY

Recanalisation therapies for wake-up stroke

Review question

Do people who wake up with new acute stroke symptoms benefit from treatments to reopen the blocked 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). This is a leading cause of death and disability worldwide. Treatments to reopen blood vessels such as clot-dissolving drugs (thrombolysis) or mechanical devices to remove blood clots (thrombectomy) 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 to be ineligible for recanalisation therapies because the time of stroke onset is unknown. However, recent studies of selected patients suggest benefit from recanalisation therapies.

Search date

We searched for randomised controlled trials (a type of study in which people are randomly allocated to one of two or more treatment groups) until 24 May 2021.

Study characteristics

We included seven trials with a total of 980 participants. Five trials with 775 wake-up stroke participants were randomised to intravenous thrombolytic treatment or to control (either placebo (dummy treatment) or standard medical treatment alone). Two trials with 205 wake-up stroke participants with a blood clot in a large brain artery were randomised to either endovascular mechanical thrombectomy plus standard medical treatment or standard medical treatment alone.

Key results

We found that recanalisation therapies can improve functional outcome and survival in selected patients with wake-up stroke. However, we cannot rule out the possibility that treatment increases the risk of bleeding in the brain. The optimal selection criteria with regard to imaging criteria or time window, or both, for choosing patients to treat is still unclear; these criteria differed between the trials. More trials to investigate this further are therefore warranted.

Quality of evidence

We judged the included trials to be at low or unclear risk of bias, and the overall certainty of the evidence as high.

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SUMMARY OF FINDINGS

Summary of findings 1. Intravenous thrombolytic treatment compared to standard medical care for wake-up stroke

Intravenous thrombolytic treatment compared to standard medical care for wake-up stroke

Patient or population: people with stroke upon awakening
Setting: hospital emergency department
Intervention: intravenous thrombolytic treatment
Comparison: standard medical care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with standard medical care	Risk with intravenous thrombolytic treatment			
Independent functional outcome at end of follow-up assessed with: mRS 0 to 2 at follow-up: 90 days	584 per 1000	660 per 1000 (590 to 736)	RR 1.13 (1.01 to 1.26)	763 (5 RCTs)	⊕⊕⊕⊕ HIGH
Symptomatic intracranial haemorrhage at follow-up: mean 90 days	5 per 1000	19 per 1000 (5 to 67)	RR 3.47 (0.98 to 12.26)	754 (4 RCTs)	⊕⊕⊕⊕ HIGH
Death at follow-up: mean 90 days	99 per 1000	67 per 1000 (43 to 106)	RR 0.68 (0.43 to 1.07)	763 (5 RCTs)	⊕⊕⊕⊕ HIGH

*__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; **RCT:** randomised controlled trial; **RR:** risk ratio

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

Summary of findings 2. Endovascular treatment compared to standard medical care for wake-up stroke

Endovascular treatment compared to standard medical care for wake-up stroke

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Patient or population: people with stroke upon awakening
Setting: hospital emergency department
Intervention: endovascular treatment
Comparison: standard medical care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard medical care	Risk with endovascular treatment				
Independent functional outcome at end of follow-up assessed with: mRS 0 to 2 at follow-up: 90 days	116 per 1000	594 per 1000 (298 to 1000)	RR 5.12 (2.57 to 10.17)	205 (2 RCTs)	⊕⊕⊕⊕ HIGH**	
Intracranial haemorrhage at follow-up: mean 90	-	-	-	-	-	Data not available from the studies.
Death at follow-up: mean 90	326 per 1000	222 per 1000 (140 to 349)	RR 0.68 (0.43 to 1.07)	205 (2 RCTs)	⊕⊕⊕⊕ HIGH**	

*__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).
**None of these RCTs could be blinded for investigators or participants due to the nature of the intervention.
CI: confidence interval;**mRS:** modified Rankin Scale; **RCT:** randomised controlled trial; **RR:** risk ratio

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

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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 of 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 to be 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); however, 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 (Roaldsen 2021; 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 upon 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). Wake-up stroke occurs when a patient wakes up with new stroke symptoms acquired during sleep.

Description of the intervention

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

Thrombolytic drugs are most commonly administrated intravenously and work by dissolving blood clots. They 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 since the first trial was published in 1995. 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 the 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 (Roaldsen 2021). Our review differs from Roaldsen 2021 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

It is important to establish the efficacy and safety of intravenous thrombolytic drugs and intra-arterial treatments in people with acute ischaemic stroke that presents upon awakening. The optimal selection criteria for treatment have not yet been established. The current review updates a previous version first published in 2014 (Lindekleiv 2014), and updated again in 2018 (Roaldsen 2018). Since the last update of this review was published, the results of several trials have been completed: four on intravenous thrombolysis (ECASS-4; EXTEND; THAWS; WAKE-UP), and two on endovascular thrombectomy (DAWN; DEFUSE 3); these results could be pooled quantitatively to evaluate the effects of these interventions.

OBJECTIVES

To assess the effects of intravenous thrombolysis and endovascular thrombectomy versus control in people with acute ischaemic stroke presenting upon awakening from sleep.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials of intravenous thrombolytic drugs or endovascular thrombectomy versus control in people with acute ischaemic stroke presenting upon awakening from sleep.

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 whilst 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 at end of follow-up.
- 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 at Cochrane Stroke's website. 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 24 May 2021) and the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 4, April 2021) in the Cochrane Library (24 May 2021) (Appendix 1).
- MEDLINE Ovid (from 1948 to 24 May 2021) (Appendix 2).
- Embase Ovid (from 1980 to 24 May 2021) (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 24 May 2021) (Appendix 4).
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch; searched 24 May 2021) (Appendix 5).
- Stroke Trials Registry, the Internet Stroke Centre (www.strokecenter.org/trials/; last search 7 December 2017) (Appendix 6).

Searching other resources

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

- screened the reference lists of relevant trials;
- contacted principal investigators of identified trials;
- used the Science Citation Index Cited Reference search for forward tracking of relevant references; and
- 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 the titles and abstracts of references obtained as a result of the searches, excluding obviously irrelevant reports. We retrieved the full-text articles for the remaining references, and two review authors (HL and MBR) independently screened the full-text articles and identified studies for inclusion, and identified and recorded reasons for exclusion of ineligible studies. Where necessary we consulted the third review author (EBM). 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;
- had developed symptomatic intracranial haemorrhage at end of follow-up.

One review author (MBR) entered the data into Review Manager 5 (Review Manager 2020). The same review author (MBR) also 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 contacted 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. We used the following criteria to assess risk of bias of the included trials, according to Section 8.5.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed risk of bias according to the following domains.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel

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- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other bias

We graded the risk of bias for each domain as low, high, 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 calculated a weighted estimate of treatment effects across trials and reported risk ratios (RRs) with 95% confidence intervals (CIs). When continuous scales of measurement were used to assess the effects of treatment, we would use the mean difference (MD). For studies that used different scales for assessment of similar outcomes, we planned 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 permit intention-to-treat analysis, we contacted the study authors to request 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 used the I^2 statistic to measure heterogeneity amongst the trials in each analysis.

We identified and measured statistical and clinical heterogeneity as recommended in Section 10.10.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

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

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

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

Assessment of reporting biases

We planned to use funnel plots to assess reporting bias if a given outcome was assessed by more than 10 studies.

Data synthesis

We used a fixed-effect model for pooled data, and considered not pooling data if we encountered considerable heterogeneity (I^2 of 80% or more) across studies.

We used 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 2021). We used GRADEpro GDT to create summary of findings tables (GRADEpro GDT).

Subgroup analysis and investigation of heterogeneity

We prespecified that in the case of sufficient data we would perform analyses for the primary outcome in the following subgroups.

- Age (under and over 60 years).
- Sex.
- National Institutes of Health Stroke Scale (NIHSS) score (under and over 10).
- Participants characterised by specific imaging criteria (e.g. large vessel occlusion absent or present).
- Participants treated at different time intervals (e.g. within three hours after first observation of stroke symptom after awakening from sleep or longer than three hours).

Sensitivity analysis

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

Summary of findings and assessment of the certainty of the evidence

We summarised the review findings in Summary of findings 1 and Summary of findings 2 using the GRADE approach, as described in Chapter 14 of the *Cochrane Handbook* (Higgins 2021). We included the following outcomes.

- Good functional outcome at end of follow-up.
- Death from all causes at end of follow-up.
- Symptomatic intracranial haemorrhage at end of follow-up.

We were not able to procure data on the following pre-planned outcomes.

- Quality of life at the end of follow-up.
- Neurological status at seven to 14 days and at the end of follow-up.

We would downgrade the certainty of evidence if deemed necessary based on the five GRADE considerations (study limitations, imprecision, inconsistency, indirectness, and publication bias) and in such cases justify all decisions to downgrade the certainty of evidence in footnotes.

RESULTS

Description of studies

We included seven randomised trials involving a total of 980 participants (DAWN; DEFUSE 3; ECASS-4; EXTEND; Michel 2012; THAWS; WAKE-UP). Five trials examined intravenous thrombolytic treatment versus control (ECASS-4; EXTEND; Michel 2012; THAWS;

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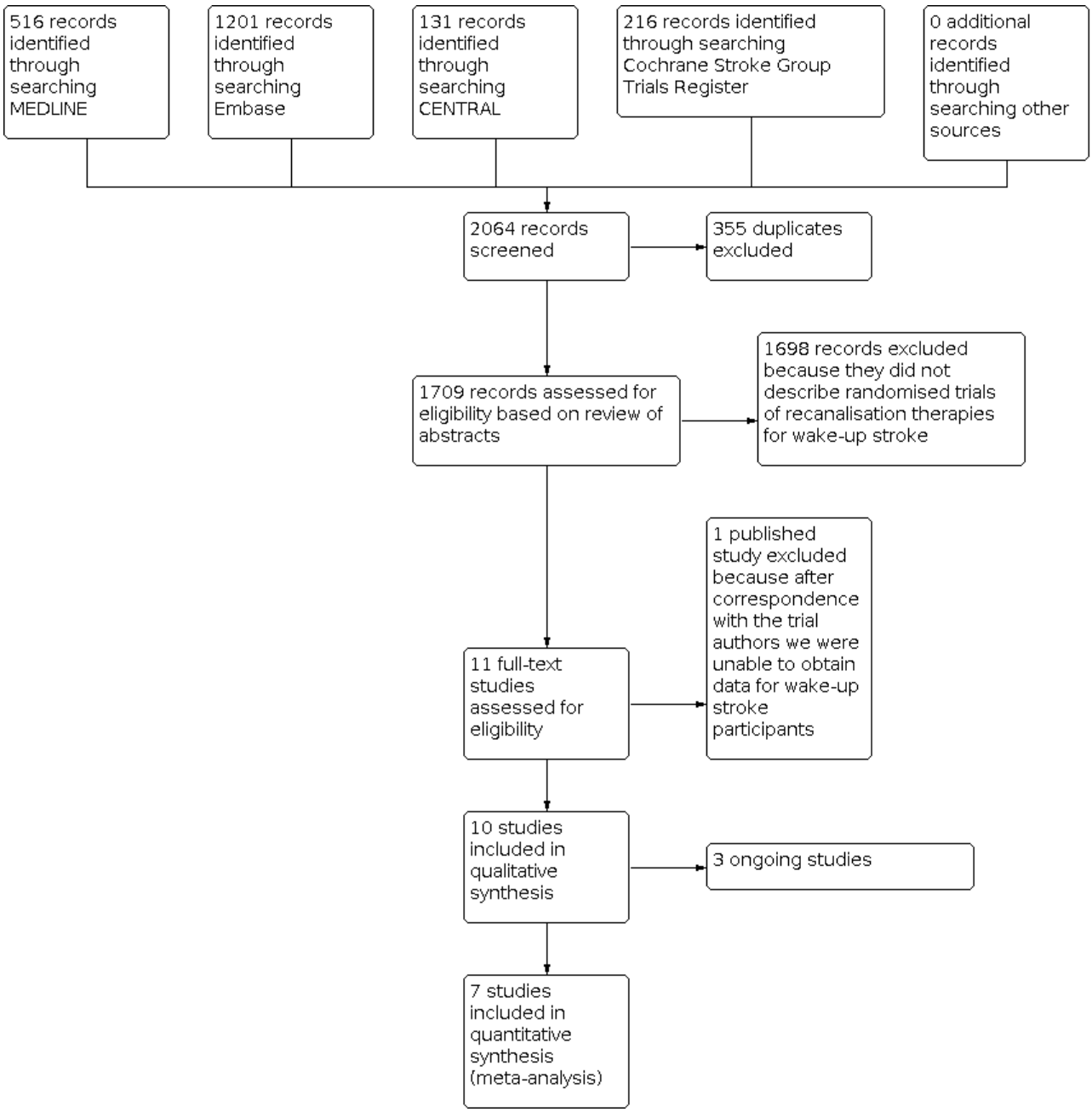
WAKE-UP), and two trials examined endovascular thrombectomy versus control (DAWN; DEFUSE 3). All trials included both participants with wake-up strokes and those with unknown onset strokes. We only included data for participants with wake-up strokes.

Results of the search

The searches yielded 2064 references. We excluded 355 duplicates that were not relevant to the review objective. We assessed a total of 1709 records, of which 1698 records were excluded because based on the abstract they were not randomised trials of wake-up stroke. We assessed 11 records in full, of which seven studies were included in the review. The PRISMA flow diagram is shown in Figure 1.

Figure 1. PRISMA flow diagram.



Included studies

The largest included study was the WAKE-UP trial, with 503 participants, of whom 449 participants had wake-up stroke and were included in the review. Patients were included in the trial based on the findings of magnetic resonance imaging diffusion-weighted imaging/fluid attenuated inversion recovery (MRI DWI/

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FLAIR) mismatch on MRI and randomised to alteplase (0.9 mg/kg) or placebo. THAWS included 131 participants, of whom 89 participants had wake-up stroke. Patients were selected by MRI DWI/FLAIR mismatch criteria and then randomised to treatment with alteplase (0.6 mg/kg) or placebo. EXTEND included 225 participants, of whom 146 participants had wake-up stroke. Patients were selected by MRI or computed tomography (CT) perfusion core/penumbra mismatch criteria and then randomised to receive alteplase (0.9 mg/kg) or placebo. ECASS-4 included 119 participants, of whom 82 participants had wake-up stroke and were included in the review. Patients were selected by MRI perfusion core/penumbra mismatch criteria and then randomised to receive alteplase (0.9 mg/kg) or placebo. The authors of Michel 2012 conducted a pilot trial including 12 participants with unknown onset of stroke, of which nine participants had wake-up stroke and were included in the review. They had signs on perfusion CT of ischaemic tissue at risk of infarction (Michel 2012); all had infarction in the middle cerebral artery territory. Of the nine participants, four were randomised to alteplase (0.9 mg/kg) and five to placebo. DAWN included 206 participants, of which 114 participants had wake-up stroke. Patients with occlusion of intracranial internal carotid artery or proximal middle cerebral artery last been known to be well six to 24 hours were randomised to thrombectomy plus standard care or to standard care alone. DEFUSE 3 included 182 participants; 50% of these participants had wake-up stroke. Patients with occlusion of internal carotid artery or proximal middle cerebral artery and an initial infarct size less than 70 mL and a penumbra ratio over 1.8 were randomised to thrombectomy plus standard medical care or to medical care alone.

Excluded studies

We excluded two studies: POSITIVE and NCT01455935 The POSITIVE investigators have not published specific information on wake-up stroke. The contact person of POSITIVE did not respond to our request to share data. NCT01455935 has been put on hold and is excluded in this review.

We identified two ongoing trials: NCT03181360 and NCT04256096.

Risk of bias in included studies

See Figure 2.

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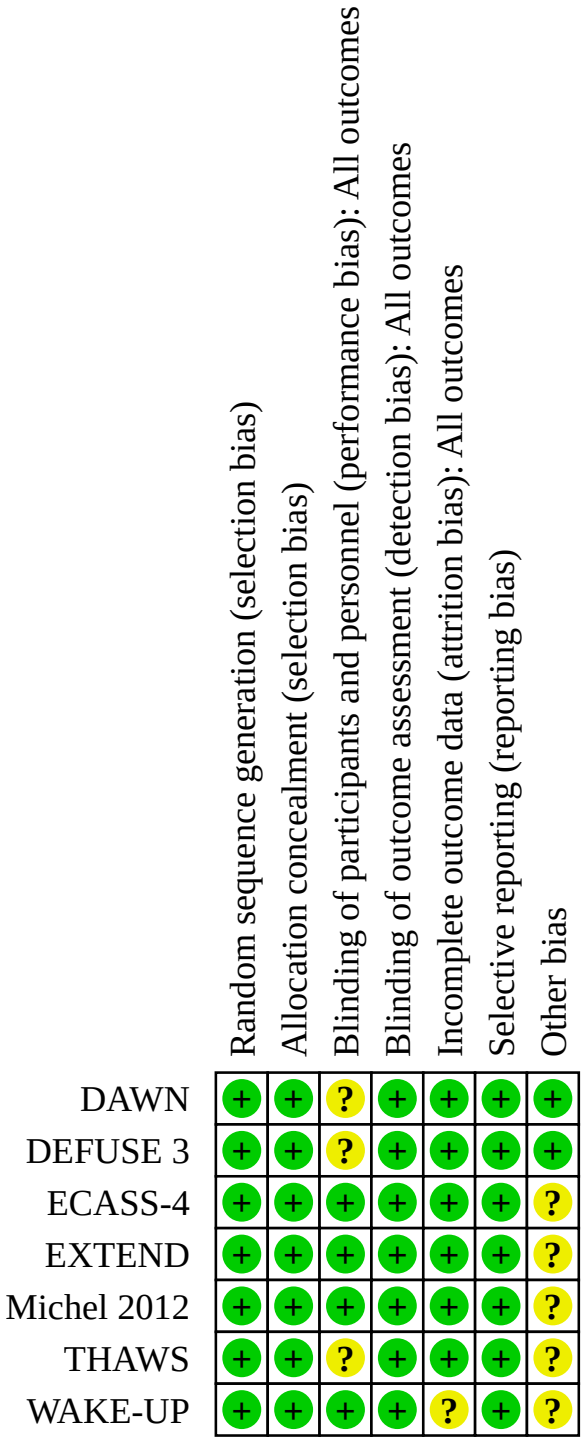
Figure 2. Risk of bias summary: judgements about each risk of bias item for the included studies.



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Allocation

The quality of randomisation was adequate in the seven included studies (DAWN; DEFUSE 3; ECASS-4; EXTEND; Michel 2012; THAWS; WAKE-UP), therefore we assessed all seven studies as at low risk of selection bias.

Blinding

We assessed all seven studies to be at low risk of bias (DAWN; DEFUSE 3; ECASS-4; EXTEND; Michel 2012; THAWS; WAKE-UP). In the trials of endovascular thrombectomy, investigators and participants could not be blinded due to the nature of the intervention. Three of the included trials did not blind the investigators or participants to the allocated treatment (DAWN; DEFUSE 3; THAWS). We cannot rule out that the open design may have introduced bias with some degree of enhancement of treatment effects. However, as the outcome measurements were blinded in all trials, we assume that any such effect would be relatively small.

Incomplete outcome data

We assessed the risk of attrition bias in the included trials to be either unclear or low. In five trials (DAWN; ECASS-4; EXTEND; Michel 2012; THAWS), no participants were lost to follow-up, therefore risk of bias was assessed as low in these trials. We assessed the risk of bias as unclear for DEFUSE 3 and WAKE-UP, for which three participants and 13 participants were lost to follow-up, respectively.

Selective reporting

We assessed all seven studies as at low risk of reporting bias (DAWN; DEFUSE 3; ECASS-4; EXTEND; Michel 2012; THAWS; WAKE-UP).

Other potential sources of bias

Six trials were prematurely terminated due to lack of funding (WAKE-UP), slow enrolment (ECASS-4), lack of equipoise (EXTEND; THAWS), or interim analyses showing efficacy (DAWN; DEFUSE 3). We assessed the risk of other bias as unclear for these studies.

Effects of interventions

See: **Summary of findings 1** Intravenous thrombolytic treatment compared to standard medical care for wake-up stroke; **Summary of findings 2** Endovascular treatment compared to standard medical care for wake-up stroke

Good functional outcome at the end of 90 days follow-up

For endovascular thrombectomy of large vessel occlusion, good functional outcome at 90 days follow-up was observed in 46% of participants randomised to endovascular thrombectomy and 9% of participants randomised to control (RR 5.12, 95% CI 2.57 to 10.17; P < 0.001; 205 participants, 2 RCTs; high-certainty evidence) (Analysis 1.1).

For intravenous thrombolytic treatment, good functional outcome (defined as mRS score 0 to 2) at 90 days follow-up was observed in 66% of participants randomised to thrombolytic treatment and 58% of participants randomised to control (risk ratio (RR) 1.13, 95% confidence interval (CI) 1.01 to 1.26; P = 0.03; 763 participants, 5 RCTs; high-certainty evidence) (Analysis 1.2).

Death at the end of 90 days follow-up

Twenty-two per cent of participants randomised to endovascular thrombectomy and 33% of participants randomised to control had died at 90 days follow-up (RR 0.68, 95% CI 0.43 to 1.07; P = 0.10; 205 participants, 2 RCTs; high-certainty evidence) (Analysis 2.1).

Data were available on intravenous thrombolytic treatment for 763 participants. Seven per cent of participants randomised to intravenous thrombolytic treatment and 10% of participants randomised to control had died at 90 days follow-up (RR 0.68, 95% CI 0.43 to 1.07; P = 0.09; 763 participants, 5 RCTs; high-certainty evidence) (Analysis 2.2).

Symptomatic intracranial haemorrhage at the end of follow-up

Data were available on intravenous thrombolytic treatment for 754 participants with ischaemic wake-up stroke from four studies (ECASS-4; EXTEND; THAWS; WAKE-UP). Symptomatic intracranial haemorrhage occurred in 3% of participants randomised to intravenous thrombolytic treatment and 1% of participants randomised to control (RR 3.47, 95% CI 0.98 to 12.26; P = 0.05; 754 participants, 4 RCTs; high-certainty evidence) (Analysis 3.1).

Quality of life at end of follow-up

We were not able to procure data on this pre-planned outcome.

Neurological status at seven to 14 days and at the end of follow-up

We were not able to procure data on this pre-planned outcome.

Subgroup analyses

Age and sex

There was similar effect of thrombolytic treatment on functional outcome in younger and older participants from the four trials that provided subgroup data on age: (RR 1.08, 95% CI 0.93 to 1.25) versus (RR 1.15, 95% CI 1.01 to 1.32) (ECASS-4; EXTEND; THAWS; WAKE-UP). The cutoff for younger and older participants was 60 years (Analysis 4.1).

There was similar effect of thrombolytic treatment on functional outcome in women and men from the four trials that provided subgroup data on sex: (RR 1.07, 95% CI 0.89 to 1.30) versus (RR 1.11, 95% CI 0.96 to 1.29) (Analysis 4.2) (ECASS-4; EXTEND; THAWS; WAKE-UP).

Stroke severity

There was similar effect of thrombolytic treatment on functional outcome in participants with higher NIHSS score and participants with lower NIHSS score from the four trials that provided subgroup data on NIHSS score (ECASS-4; EXTEND; THAWS; WAKE-UP), although the confidence interval was wider for participants with higher NIHSS score: (RR 1.38, 95% CI 0.88 to 2.16) versus (RR 1.08, 95% CI 0.99 to 1.19). The cutoff for NIHSS score was 10 (Analysis 4.3).

Large vessel occlusion diagnosed on imaging

There was similar effect of thrombolytic treatment on functional outcome for participants with large vessel occlusion and no large vessel occlusion present on imaging: (RR 1.31, 95% CI 0.93 to 1.85)

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versus (RR 1.12, 95% CI 1.01 to 1.24) (Analysis 4.4) (EXTEND; THAWS; WAKE-UP).

Time from first observation of symptoms to onset of treatment

There was similar effect of thrombolytic treatment on functional outcome in participants treated within three hours after awakening and those treated more than three hours after awakening from the three trials that provided subgroup data on time from first observation of symptoms to onset of treatment: (RR 1.06, 95% CI 0.90 to 1.24) versus (RR 1.12, 95% CI 0.96 to 1.32) (Analysis 4.5) (ECASS-4; THAWS; WAKE-UP).

Sensitivity analyses

The sensitivity analysis using a random-effects model (Analysis 5.1; Analysis 5.2) found similar results compared to the fixed-effect model (Analysis 1.1; Analysis 1.2) for the primary outcome.

DISCUSSION

The meta-analysis showed a strong positive effect of thrombectomy on functional outcome after three months (RR 5.12, 95% CI 2.57 to 10.17) in selected patients with wake-up stroke and large vessel occlusion in the anterior circulation treated in the six- to 24-hour time window. The effect estimate for participants with wake-up stroke was larger than in previous analyses where all patients were included. In comparison, the corresponding risk ratio in DEFUSE 3 was 2.67 (95% CI 1.60 to 4.48) when all 192 participants (of whom 91 had wake-up stroke) were included. In DAWN, the proportion with good functional outcome was 49% in the thrombectomy group and 13% in the control group when all 206 participants (114 with wake-up stroke) were included. The reason for the larger effect seen in wake-up stroke patients is unknown, but one might speculate that the onset of stroke symptoms in patients with wake-up stroke is more likely to be in the lower spectrum of the six- to 24-hour window than in the higher spectrum. The circadian variation in ischaemic stroke occurrence, with a peak late in the morning, as well as circadian variations of potential triggers such as blood pressure, paroxysmal atrial fibrillation, and platelet aggregability, support the assumption that wake-up strokes are likely to occur close to awakening.

The effect of intravenous thrombolytic treatment in wake-up stroke in the meta-analysis was moderate (RR 1.13, 95% CI 1.01 to 1.26) and lower than the effect seen in the WAKE-UP trial, which contributed the largest number of participants. In WAKE-UP, 53% of participants in the alteplase group and 42% in the placebo group achieved a favourable outcome, defined as mRS 0 to 1, a difference in treatment effect which is comparable to that seen in patients treated within three hours after stroke onset (Emberson 2014). However, this was substantially weakened when the results from all trials were combined. Symptomatic intracranial haemorrhage occurred in 3% of participants treated with thrombolysis and 1% of controls. The increased risk of symptomatic intracranial haemorrhage in participants treated with thrombolysis was of borderline statistical significance (RR 3.47, 95% CI 0.98 to 12.26; P = 0.05), but this did not outweigh the positive effect of thrombolytic treatment on the main functional outcome.

It is important to note that all included trials on thrombolysis were terminated early, which is a potential source of bias. WAKE-UP was terminated early due to lack of funding, and ECASS-4 because of slow enrolment. EXTEND and THAWS were prematurely terminated after the publication of results from WAKE-UP. Our results must therefore be interpreted with caution due to loss of statistical power and because of a potential source of bias due to a positive result.

It should be noted that the study participants present in the included analyses may not be representative of all patients with ischaemic wake-up stroke. All trials used either MRI DWI/FLAIR mismatch criteria or MRI or CT perfusion penumbra for the selection of participants. In WAKE-UP, 859 of the 1362 patients who were screened for inclusion were excluded, 455 of them due to lack of DWI/FLAIR mismatch criteria. Patients with lacunar strokes, shown to benefit from treatment in WAKE-UP, will not be identified by penumbra imaging (Thomalla 2020). Further trials are warranted to identify the optimal criteria for selecting patients with wake-up stroke to treatment.

Summary of main results

Recanalisation therapies with endovascular thrombectomy of large vessel occlusion in the anterior circulation and thrombolytic treatment with intravenous alteplase seem to be safe and effective treatments in highly selected patients with wake-up stroke.

Overall completeness and applicability of evidence

The participants in the studies included in this review may not be representative of all patients with ischaemic wake-up stroke. There is high-certainty evidence that intravenous thrombolytic treatment improves functional and neurological outcomes without increasing death in selected patients with wake-up stroke, and there is high-certainty evidence that endovascular thrombectomy treatment of large vessel occlusion in the anterior circulation substantially improves functional and neurological outcomes without increasing death in selected patients with wake-up stroke. The meta-analysis showed a strong positive effect of endovascular thrombectomy on functional outcome after three months (RR 5.12, 95% CI 2.57 to 10.17) in selected patients with wake-up stroke and large vessel occlusion in the anterior circulation who were treated in the six- to 24-hour time window. The effect of intravenous thrombolytic treatment in wake-up stroke in this meta-analysis was more moderate (RR 1.13, 95% CI 1.01 to 1.26).

Quality of the evidence

We prepared summary of findings tables using GRADEpro GDT and Cochrane methods (GRADEpro GDT).

The strengths of this review are that all studies were either at a low or unclear risk of bias and the use of a standardised main outcome assessment. A common source of heterogeneity in systematic reviews is differences in follow-up time. All of the included studies measured outcomes at 90 days follow-up.

The weaknesses of this review are that some studies were small, and studies included different types of advanced imaging criteria for the selection of patients to treatment. Participants and investigators in three of the included trials were not blinded to the allocated treatment (DAWN; DEFUSE 3; THAWS). Another weakness is that all included trials, except the small pilot trial (Michel 2012), were terminated prematurely and therefore lack statistical power. Causes given for premature termination of the included trials were interim analyses showing efficacy (DAWN; DEFUSE 3); lack of equipoise or slow recruitment (ECASS-4; EXTEND; THAWS); or lack of funding (WAKE-UP).

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Potential biases in the review process

A strength of this review is that is has received unpublished data from several of the included studies; this applies for all included studies on intravenous thrombolytic treatment for wake-up stroke. Another strength is that all of the included studies performed follow-up at the same time interval, that is 90 days. This systematic review also has some limitations. A limited number of studies were available for inclusion, and the number of included participants was rather low. Potential biases in the review process were minimised by searching for published and unpublished studies from several sources with no restriction on date of publication or language. Two review authors independently extracted data and conducted the risk of bias assessment. The findings and conclusions of this review are affected by the quality, quantity, and outcome reporting of all of the included trials.

Agreements and disagreements with other studies or reviews

We identified a number of systematic reviews and meta-analyses on thrombolytic treatment for ischaemic wake-up stroke. Buck and colleagues performed a systematic review of 11 studies (one RCT, three case reports/series, and seven observational studies), but did not perform any statistical analysis because of considerable heterogeneity of the reported methods and data (Buck 2014). Thomalla 2020, a meta-analysis of individual patient data from ECASS-4, EXTEND, THAWS, and WAKE-UP, found a stronger effect estimate for the primary outcome of mRS 0 to 1 than we did for the primary outcome of mRS 0 to 2 in the current review. A recently published comprehensive review and meta-analysis on thrombolytic treatment for wake-up stroke included two RCTs (THAWS; WAKE-UP), five comparative cohort studies, and nine non-comparative single-group studies (Mac Grory 2021). We were unable to identify any previous meta-analyses on endovascular thrombectomy treatment in wake-up stroke patients.

AUTHORS' CONCLUSIONS

Implications for practice

There is good evidence that intravenous thrombolytic treatment improves functional and neurological outcomes without increasing death in selected patients with wake-up stroke. There is also good evidence that endovascular thrombectomy treatment substantially improves functional and neurological outcomes without increasing death in selected patients with wake-up stroke.

Implications for research

Several trials are ongoing, and their results might confirm already-published results as well as further explore whether a larger proportion of wake-up stroke patients can safely receive an effective acute treatment.

All of the trials included in this review with the exception of Michel 2012 were terminated early. Plans for interim analyses and stopping guidelines varied between trials or were not described in study protocols. Future trials should be designed in order to reduce the risk of early termination, and plans for interim analyses and stopping guidelines should be explicitly stated in the study protocol (Task Force of the Working Group 1994).

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CHARACTERISTICS OF STUDIES

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

DAWN

Study characteristics	
Methods	International, multicentre, prospective, randomised, open-label trial with blinded assessment of end-points
Participants	Patients were eligible for inclusion if they had evidence of occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both on CTA or MRA. They also needed to have a clinical/radiological mismatch between the severity of the clinical deficit and the infarct volume.

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DAWN *(Continued)*

	Patients must have clinical signs and symptoms consistent with the diagnosis of an acute ischaemic stroke, and belong to 1 of the following subgroups: patient has failed IV t-PA therapy (defined as a confirmed persistent occlusion 60 min after administration); patient is contraindicated for IV t-PA administration. Age ≥ 18 years Baseline NIHSS ≥ 10 (assessed within 1 hour prior to measuring core infarct volume) Patient can be randomised between 6 and 24 hours after time last known well. No significant pre-stroke disability (pre-stroke mRS must be 0 or 1) Infarction < 1/3 MCA territory involved, as evidenced by CT or MRI
Interventions	Thrombectomy (treatment group) versus standard medical care (control group)
Outcomes	Primary endpoint was mean score of mRS at 90 days.
Notes	Funding source: Stryker Neurovascular. Terminated prematurely due to efficacy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was central and a web-based procedure with block minimisation to balance the 2 treatment groups, and was stratified according to mismatch criteria, the interval between the time that the participant was last known to be well and randomisation.
Allocation concealment (selection bias)	Low risk	Web-based randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded assessment of endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	No participants lost to follow-up, and intention-to-treat analysis provided
Other bias	Low risk	At 31 months and 206 participants enrolled, the trial was stopped because of the results of a prespecified interim analysis. Adaptive trial design with sample size from 150 to 500 participants

DEFUSE 3

Study characteristics

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DEFUSE 3 *(Continued)*

Methods	Multicentre, randomised, open-label trial with blinded outcome assessment
Participants	Patients with acute ischaemic stroke presenting between 6 and 16 hours from last known well and with remaining brain tissue that was not yet infarcted. Patients with proximal MCA or ICA occlusion, an initial infarct size of less than 70 mL, and a ratio of the volume of the ischaemic tissue on perfusion imaging to infarct volume of 1.8 or more
Interventions	Endovascular thrombectomy plus standard medical treatment versus standard medical treatment alone
Outcomes	Primary outcome was the ordinal score on the mRS at day 90 follow-up. Secondary outcome was functional independence mRS 0 to 2 at day 90. Primary safety outcome was death within 90 days and the occurrence of symptomatic intracerebral haemorrhage within 36 hours.
Notes	Funding source: National Institute of Neurological Disorders and Stroke

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based, dynamic randomisation system. Stratified according to age, core infarct volume, time from symptom onset to enrolment, baseline NIHSS, and trial site
Allocation concealment (selection bias)	Low risk	Computer-based, dynamic randomisation system. Stratified according to age, core infarct volume, time from symptom onset to enrolment, baseline NIHSS, and trial site
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Outcome assessed by certified rater who was blinded to trial assignment. Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded endpoint assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants lost to follow-up, and intention-to-treat analysis provided
Selective reporting (reporting bias)	Low risk	Intention-to-treat analysis provided.
Other bias	Low risk	After an early interim analysis after the DAWN trial results and after 182 randomised participants, the trial was halted due to efficacy. Maximal sample size calculated to 476 participants.

ECASS-4

Study characteristics

Methods	Randomised, multicentre, double-blind, placebo-controlled, phase 3 trial

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ECASS-4 *(Continued)*

Participants	Patients with acute ischaemic stroke could be included if treatment could be started within 4.5 to 9 hours after symptom onset. Patients who woke up with stroke symptoms could be included if the mean between time last seen well and symptom recognition was between these limits. The NIHSS score had to be between 4 and 26, and the penumbral MRI had to demonstrate a perfusion volume (PWI) to infarct core (DWI) ratio of 1.2, and a perfusion lesion minimum volume of 20 ml.The trial included 119 participants, of whom 63 had wake-up stroke. The study authors contributed unpublished data on participants with wake-up stroke.
Interventions	Participants were randomised to either intravenous thrombolysis with rt-PA, alteplase (0.9 mg/kg) or placebo.
Outcomes	Primary endpoint was categorical shift in the mRS at day 90. Secondary endpoints were favourable outcome mRS 0 to 1 versus unfavourable outcome 2 to 6, improvement of neurological status measured by NIHSS, reperfusion at 12 to 24 hours after treatment.
Notes	Funding source: no financial support for the research, authorship, or publication of main article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Web-based randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind and placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Intention-to-treat analysis was provided.
Other bias	Unclear risk	Stopped early because of slow recruitment after 119 of 264 planned participants

EXTEND

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial
Participants	225 participants, of whom 146 had wake-up stroke. The study authors contributed unpublished data on participants with wake-up stroke.

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EXTEND *(Continued)*

Inclusion criteria

- Patients presenting with acute ischaemic stroke
- Patient, family member, or legally responsible person depending on local ethics requirements has given informed consent
- Age ≥ 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 awoke with stroke may be included if neurological and other exclusion criteria are satisfied. 'Wake-up' stroke 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 PWI lesion volume to 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

- 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 MCA 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). 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 or low-dose aspirin, or both) 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

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EXTEND *(Continued)*

Interventions	• Intravenous t-PA (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
Notes	ClinicalTrials.gov identifier: NCT01580839 (Australian part) and NCT00887328 (international part) Funding source: supported by Australian National Health and Medical Research Council and the Commonwealth Scientific and Industrial Research Organization Flagship Program. In Taiwan: Ministry of Health and Welfare Grant and the Ministry of Science and Technology Taiwan Clinical Trial Consortium for Stroke. Terminated due to lack of equipoise after 225 of 310 planned participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Web-based randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind and placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Intention-to-treat analysis was provided.
Other bias	Unclear risk	Terminated prematurely due to lack of equipoise

Michel 2012

Study characteristics

Methods	Randomised, double-blinded, placebo-controlled pilot trial
Participants	12 participants with a supratentorial stroke of unknown onset in the MCA territory and significant volume of at-risk tissue on perfusion CT. 9 participants had wake-up stroke, and 3 had a non-wake-up stroke of unknown onset. The study authors contributed unpublished data for the 9 participants with wake-up stroke.
Interventions	• Intravenous t-PA (alteplase) 0.9 mg/kg body weight up to a maximum of 90 mg, 10% as bolus, 90% over 1 hour as infusion

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Michel 2012 *(Continued)*

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

THAWS

Study characteristics

Methods	Randomised, single-blinded, controlled trial
Participants	131 participants, of whom 89 had wake-up stroke. The study authors contributed unpublished data on participants with wake-up stroke. **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

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THAWS *(Continued)*

Exclusion criteria

- Pre-stroke mRS > 1 (patients who are unable to carry out all daily activities and require some help or supervision)
- Contraindications in the Japanese guideline for the intravenous application of rt-PA (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
- Blood glucose < 50 mg/dL or > 400 mg/dL
- Platelet count ≤ 100,000/mm^3
- INR 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 t-PA (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
Notes	ClinicalTrials.gov identifier: NCT02002325 Funding Source: Japan Agency for Medical Research and Development and the Ministry of Health, Labour, and Welfare, and partly by the Mihara Cerebrovascular Disorder Research Promotion Fund. Terminated due to lack of equipoise after 131 of 300 planned participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Web-based randomisation

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THAWS *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Intention-to-treat analysis was provided.
Other bias	Unclear risk	Terminated prematurely because of lack of equipoise after the WAKE-UP trial published their results

WAKE-UP

Study characteristics	
Methods	Randomised, double-blinded, placebo-controlled trial
Participants	503 participants, of whom 449 had wake-up stroke. The study authors contributed unpublished data on participants with wake-up stroke. **Clinical inclusion criteria** • Clinical diagnosis of acute ischaemic stroke with unknown symptom onset (e.g. stroke symptoms recognised upon 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) • 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

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WAKE-UP *(Continued)*

- Pregnancy or lactating (formal testing needed in women 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 the 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
- 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 MCA 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 t-PA (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
Notes	ClinicalTrials.gov identifier: NCT01525290

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WAKE-UP *(Continued)*

	Funding Source: supported by a grant (278276) from the European Union Seventh Framework Program. Trial was terminated after 503 participants of the estimated and planned 800 target sample size for financial reasons.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Web-based randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13 participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Intention-to-treat analysis was provided.
Other bias	Unclear risk	Trial was terminated after 503 participants of the estimated and planned 800 target sample size for financial reasons.

aPTT: activated partial thromboplastin time
ASPECTS: Alberta Stroke Program Early Computed Tomography Score
CT: computed tomography
CTA: computed tomography angiography
DWI: diffusion-weighted imaging
FLAIR: fluid attenuated inversion recovery
ICA: internal carotid artery
INR: international normalised ratio
IV: intravenous
MCA: middle cerebral artery
MRA: magnetic resonance angiogram
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
PWI: perfusion-weighted imaging
rt-PA: recombinant tissue plasminogen activator
t-PA: tissue plasminogen activator

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

Study	Reason for exclusion
NCT01455935	NCT01455935 has been put on hold and we were unable to obtain data from this study

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Study	Reason for exclusion
POSITIVE	The POSITIVE investigators have not published specific information on wake-up stroke. The contact person of POSITIVE did not respond to our request to share data

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

NCT03181360

Study name	Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST)
Methods	PROBE; prospective, randomised, open, blinded-endpoint
Participants	600 participants **Inclusion criteria** • Stroke symptoms on awakening that were not present before sleep • Clinical diagnosis of stroke with limb weakness with an NIHSS score ≥ 3, 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 (according to national/local ethics requirements) **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: o infarction comprising more than > 1/3 of the middle cerebral artery territory on plain CT or CT perfusion; o intracranial haemorrhage, structural brain lesions that can mimic stroke (e.g. cerebral tumour). • 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 antagonist 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 with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, eucarin 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)

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NCT03181360 *(Continued)*

	• 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 (recombinant fibrin-specific tissue plasminogen activator) is given as a single-dose intravenous injection 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 assessed by the mRS on the ordinal scale 0 to 6 **Secondary outcome measures** *Clinical events:* • Favourable functional outcome: mRS 0 to 1 • Good functional outcome: mRS 0 to 2 • Death from all cause during follow-up • Any intracranial haemorrhage during follow-up • Symptomatic intracranial haemorrhage by SITS-MOST definition • Symptomatic intracranial haemorrhage by IST-3 definition • Parenchymal haemorrhage type 2 • Stroke progression during follow-up • Recurrent ischaemic stroke during follow-up • Major extra cranial bleeding • NIHSS score at 24 hours and day 7 • Change in NIHSS score from baseline to 24 hours and day 7 *Other clinical outcomes at 3 months:* • NIHSS score • Barthel Index score • EuroQol score • MMSE scores *Health-economic variables:* • Length of hospital stay • Nursing home care after discharge • Rehospitalisations during first 3 months
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 Funding source: main source is the Norwegian Program for Clinical Research Therapy initiated by the Norwegian Ministry of Health and Care Services and financed through the Norwegian National Budget. Additional grants from the Swiss Heart Foundation, the British Heart Foundation, and the National Association for Public Health. The costs of tenecteplase are covered by an unconditional grant from Boehringer Ingelheim.

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NCT04256096

Study name	Randomization of Endovascular Treatment in Acute Ischemic Stroke in the Extended Time Window (RESILIENTExt)
Methods	A phase III, randomised, multicentre, open-label clinical trial that will examine whether endovascular treatment is superior to standard medical therapy alone in patients who suffer a large vessel anterior circulation ischaemic stroke within 8 to 24 hours from time last seen well
Participants	• Acute ischaemic stroke where patient is ineligible for IV thrombolytic treatment, or the treatment is contraindicated (e.g. patient presents beyond recommended time from symptom onset), or where patient has received IV thrombolytic therapy without clinical improvement • No significant pre-stroke functional disability (mRS ≤ 2) • Baseline NIHSS score obtained prior to randomisation must be ≥ 8 points (assessed within 1 hour prior to qualifying imaging) • Age ≥ 18 years (no upper age limit) • Occlusion (TICI 0 to 1) of the intracranial ICA (distal ICA or T occlusions) and/or MCA-M1 segment suitable for endovascular treatment, as evidenced by CTA, MRA, or angiogram, with or without concomitant cervical carotid occlusion or stenosis • Patient treatable within 6 to 24 hours of symptom onset. Symptom onset is defined as point in time the patient was last seen well (at baseline). Treatment start is defined as arterial puncture. • Informed consent obtained from patient or acceptable patient surrogate • Estimated enrolment is 376 participants
Interventions	Endovascular treatment of large vessel occlusion (mechanical thrombectomy) with stent-retriever and/or thromboaspiration (neurointerventionalist choice)
Outcomes	Distribution of the mRS scores at 90 days (shift analysis). The score ranges from 0 to 6, with higher values indicating a worst functional outcome at 90 days.
Starting date	9 March 2020
Contact information	Sheila CO Martins MD, PhD
Notes	ClinicalTrials.gov identifier: NCT04256096

aPTT: activated partial thromboplastin time
ASPECTS: Alberta Stroke Program Early Computed Tomography Score
CT: computed tomography
CTA: Computed tomography angiography
DWI: diffusion-weighted imaging
FLAIR: fluid attenuated inversion recovery
ICA: internal carotid artery
INR: international normalised ratio
IST-3: International Stroke Trial-3
IV: intravenous
MCA: middle cerebral artery
MMSE: Mini-Mental State Exam
MRA: magnetic resonance angiogram
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
PWI: perfusion-weighted imaging
SITS-MOST: Safe Implementation of Thrombolysis in Stroke-Monitoring Study
TICI: thrombolysis in cerebral infarction

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DATA AND ANALYSES

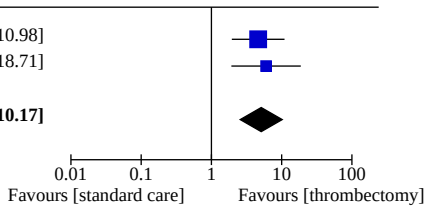
Comparison 1. Good functional outcome (modified Rankin Scale score 0 to 2) at 90 days follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Endovascular treatment	2	205	Risk Ratio (M-H, Fixed, 95% CI)	5.12 [2.57, 10.17]
1.2 Intravenous thrombolysis	5	763	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.01, 1.26]

Analysis 1.1. Comparison 1: Good functional outcome (modified Rankin Scale score 0 to 2) at 90 days follow-up, Outcome 1: Endovascular treatment

Study or Subgroup	Endovascular treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DAWN	33	67	5	47	64.5%	4.63 [1.95 , 10.98]
DEFUSE 3	21	49	3	42	35.5%	6.00 [1.92 , 18.71]
Total (95% CI)		**116**		**89**	**100.0%**	**5.12 [2.57 , 10.17]**
Total events:	54		8			

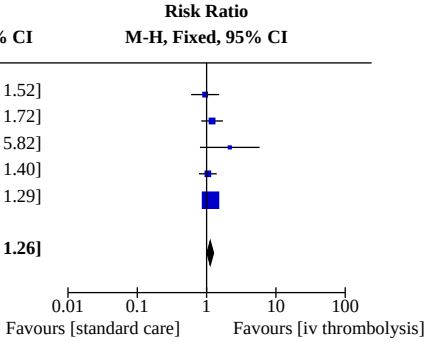
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 4.66 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Good functional outcome (modified Rankin Scale score 0 to 2) at 90 days follow-up, Outcome 2: Intravenous thrombolysis

Study or Subgroup	Intravenous thrombolysis Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ECASS-4	19	42	19	40	8.7%	0.95 [0.60 , 1.52]
EXTEND	36	73	30	73	13.4%	1.20 [0.84 , 1.72]
Michel 2012	4	4	2	5	1.0%	2.16 [0.80 , 5.82]
THAWS	35	51	25	38	12.8%	1.04 [0.78 , 1.40]
WAKE-UP	164	220	142	217	64.0%	1.14 [1.01 , 1.29]
Total (95% CI)		**390**		**373**	**100.0%**	**1.13 [1.01 , 1.26]**
Total events:	258		218			

Heterogeneity: Chi² = 2.57, df = 4 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Not applicable



Comparison 2. Death at 90 days follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Endovascular treatment	2	205	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.43, 1.07]
2.2 Intravenous thrombolysis	5	763	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.43, 1.07]

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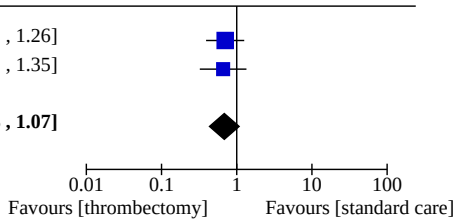
Analysis 2.1. Comparison 2: Death at 90 days follow-up, Outcome 1: Endovascular treatment

Study or Subgroup	Endovascular Events	Endovascular Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DAWN	16	67	16	47	57.3%	0.70 [0.39 , 1.26]
DEFUSE 3	10	49	13	42	42.7%	0.66 [0.32 , 1.35]
Total (95% CI)		**116**		**89**	**100.0%**	**0.68 [0.43 , 1.07]**
Total events:	26		29			

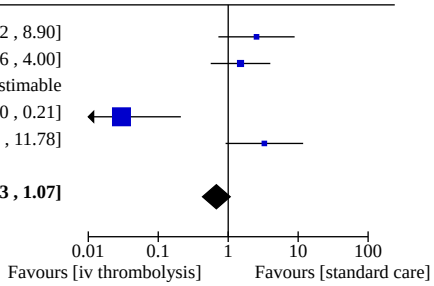
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Death at 90 days follow-up, Outcome 2: Intravenous thrombolysis

Study or Subgroup	Intravenous thrombolysis Events	Intravenous thrombolysis Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ECASS-4	8	42	3	40	7.5%	2.54 [0.72 , 8.90]
EXTEND	9	73	6	73	14.7%	1.50 [0.56 , 4.00]
Michel 2012	0	4	0	5		Not estimable
THAWS	1	51	25	38	70.3%	0.03 [0.00 , 0.21]
WAKE-UP	10	220	3	217	7.4%	3.29 [0.92 , 11.78]
Total (95% CI)		**390**		**373**	**100.0%**	**0.68 [0.43 , 1.07]**
Total events:	28		37			

Heterogeneity: Chi² = 22.49, df = 3 (P < 0.0001); I² = 87%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable



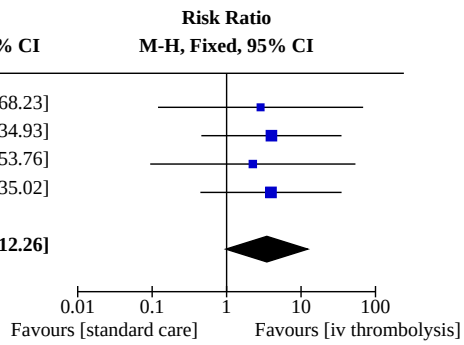
Comparison 3. Symptomatic intracranial haemorrhage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Intravenous thrombolysis	4	754	Risk Ratio (M-H, Fixed, 95% CI)	3.47 [0.98, 12.26]

Analysis 3.1. Comparison 3: Symptomatic intracranial haemorrhage, Outcome 1: Intravenous thrombolysis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ECASS-4	1	42	0	40	16.6%	2.86 [0.12 , 68.23]
EXTEND	4	73	1	73	32.4%	4.00 [0.46 , 34.93]
THAWS	1	51	0	38	18.5%	2.25 [0.09 , 53.76]
WAKE-UP	4	220	1	217	32.6%	3.95 [0.44 , 35.02]
Total (95% CI)		**386**		**368**	**100.0%**	**3.47 [0.98 , 12.26]**
Total events:	10		2			

Heterogeneity: Chi² = 0.12, df = 3 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Not applicable



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Comparison 4. Subgroup analyses for good functional outcome after intravenous thrombolytic treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Age	4	754	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.02, 1.26]
4.1.1 Young age (<= 60 years old)	4	169	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.93, 1.25]
4.1.2 Old age (> 60 years old)	4	585	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.01, 1.32]
4.2 Sex	4	754	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.98, 1.23]
4.2.1 Women	4	338	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.89, 1.30]
4.2.2 Men	4	416	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.96, 1.29]
4.3 NIHSS score	4	754	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [1.01, 1.23]
4.3.1 Low NIHSS (<= 10)	4	530	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.99, 1.19]
4.3.2 High NIHSS (> 10)	4	224	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.88, 2.16]
4.4 Findings on imaging	3	672	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.04, 1.28]
4.4.1 Large vessel occlusion present	3	213	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.93, 1.85]
4.4.2 Large vessel occlusion absent	3	459	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [1.01, 1.24]
4.5 Time from first observation of symptoms to onset of treatment	3	600	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.98, 1.22]
4.5.1 <= 3 hours	3	250	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.90, 1.24]
4.5.2 > 3 hours	3	350	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.96, 1.32]

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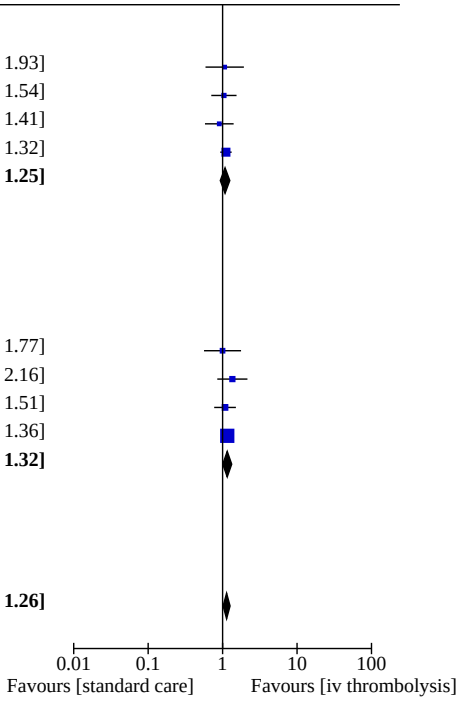
Analysis 4.1. Comparison 4: Subgroup analyses for good functional outcome after intravenous thrombolytic treatment, Outcome 1: Age

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Young age (<= 60 years old)						
ECASS-4	4	5	6	8	2.1%	1.07 [0.59 , 1.93]
EXTEND	9	11	11	14	4.4%	1.04 [0.70 , 1.54]
THAWS	6	7	4	4	2.5%	0.90 [0.58 , 1.41]
WAKE-UP	51	60	46	60	20.9%	1.11 [0.93 , 1.32]
Subtotal (95% CI)		**83**		**86**	**30.0%**	**1.08 [0.93 , 1.25]**
Total events:	70		67			
Heterogeneity: Chi² = 0.75, df = 3 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
4.1.2 Old age (> 60 years old)						
ECASS-4	15	37	13	32	6.3%	1.00 [0.56 , 1.77]
EXTEND	27	62	19	59	8.9%	1.35 [0.85 , 2.16]
THAWS	31	46	20	32	10.7%	1.08 [0.77 , 1.51]
WAKE-UP	113	160	96	157	44.1%	1.16 [0.98 , 1.36]
Subtotal (95% CI)		**305**		**280**	**70.0%**	**1.15 [1.01 , 1.32]**
Total events:	186		148			
Heterogeneity: Chi² = 0.85, df = 3 (P = 0.84); I² = 0%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Total (95% CI)		**388**		**366**	**100.0%**	**1.13 [1.02 , 1.26]**
Total events:	256		215			
Heterogeneity: Chi² = 2.15, df = 7 (P = 0.95); I² = 0%						
Test for overall effect: Z = 2.27 (P = 0.02)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						



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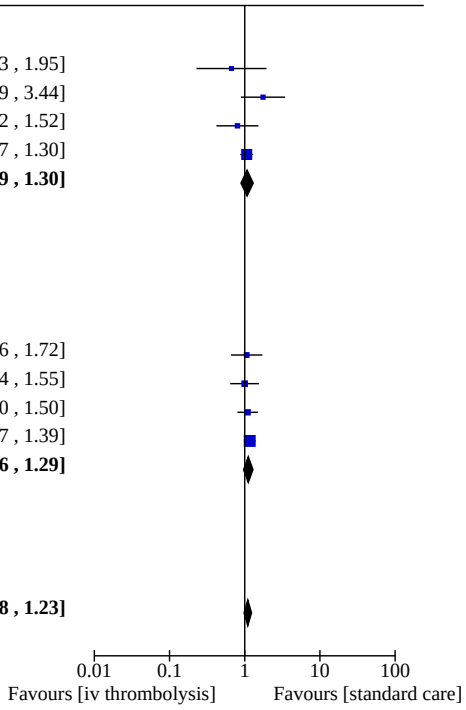
Analysis 4.2. Comparison 4: Subgroup analyses for good functional outcome after intravenous thrombolytic treatment, Outcome 2: Sex

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Women						
ECASS-4	4	17	6	17	2.9%	0.67 [0.23 , 1.95]
EXTEND	17	34	8	28	4.2%	1.75 [0.89 , 3.44]
THAWS	8	17	10	17	4.8%	0.80 [0.42 , 1.52]
WAKE-UP	49	71	89	137	29.4%	1.06 [0.87 , 1.30]
Subtotal (95% CI)		**139**		**199**	**41.4%**	**1.07 [0.89 , 1.30]**
Total events:	78		113			
Heterogeneity: Chi² = 3.59, df = 3 (P = 0.31); I² = 16%						
Test for overall effect: Z = 0.75 (P = 0.45)						
4.2.2 Men						
ECASS-4	15	25	13	23	6.5%	1.06 [0.66 , 1.72]
EXTEND	19	39	22	45	9.9%	1.00 [0.64 , 1.55]
THAWS	29	36	14	19	8.9%	1.09 [0.80 , 1.50]
WAKE-UP	115	149	53	80	33.4%	1.16 [0.97 , 1.39]
Subtotal (95% CI)		**249**		**167**	**58.6%**	**1.11 [0.96 , 1.29]**
Total events:	178		102			
Heterogeneity: Chi² = 0.54, df = 3 (P = 0.91); I² = 0%						
Test for overall effect: Z = 1.47 (P = 0.14)						
Total (95% CI)		**388**		**366**	**100.0%**	**1.10 [0.98 , 1.23]**
Total events:	256		215			
Heterogeneity: Chi² = 4.33, df = 7 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² = 0%						



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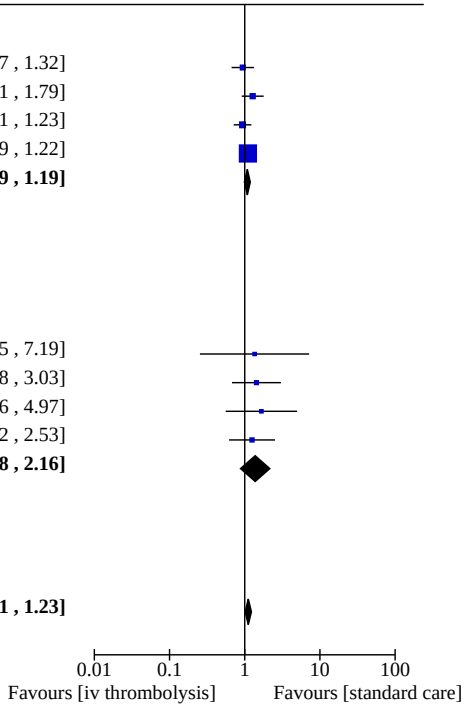
Analysis 4.3. Comparison 4: Subgroup analyses for good functional outcome after intravenous thrombolytic treatment, Outcome 3: NIHSS score

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Low NIHSS (<= 10)						
ECASS-4	16	22	17	22	7.7%	0.94 [0.67 , 1.32]
EXTEND	22	29	22	37	8.8%	1.28 [0.91 , 1.79]
THAWS	32	44	21	27	11.8%	0.94 [0.71 , 1.23]
WAKE-UP	152	179	131	170	60.8%	1.10 [0.99 , 1.22]
Subtotal (95% CI)		**274**		**256**	**89.1%**	**1.08 [0.99 , 1.19]**
Total events:	222		191			
Heterogeneity: Chi² = 2.80, df = 3 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.73 (P = 0.08)						
4.3.2 High NIHSS (> 10)						
ECASS-4	3	20	2	18	1.0%	1.35 [0.25 , 7.19]
EXTEND	14	44	8	36	4.0%	1.43 [0.68 , 3.03]
THAWS	5	9	3	9	1.4%	1.67 [0.56 , 4.97]
WAKE-UP	12	41	11	47	4.6%	1.25 [0.62 , 2.53]
Subtotal (95% CI)		**114**		**110**	**10.9%**	**1.38 [0.88 , 2.16]**
Total events:	34		24			
Heterogeneity: Chi² = 0.20, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 1.40 (P = 0.16)						
Total (95% CI)		**388**		**366**	**100.0%**	**1.12 [1.01 , 1.23]**
Total events:	256		215			
Heterogeneity: Chi² = 4.34, df = 7 (P = 0.74); I² = 0%						
Test for overall effect: Z = 2.22 (P = 0.03)						
Test for subgroup differences: Chi² = 1.06, df = 1 (P = 0.30), I² = 5.4%						



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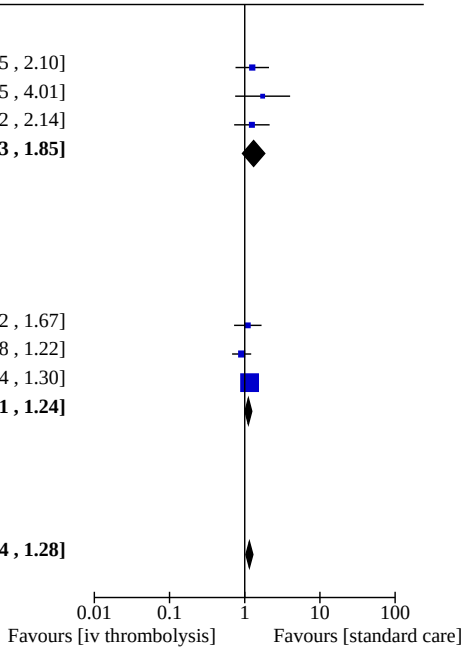
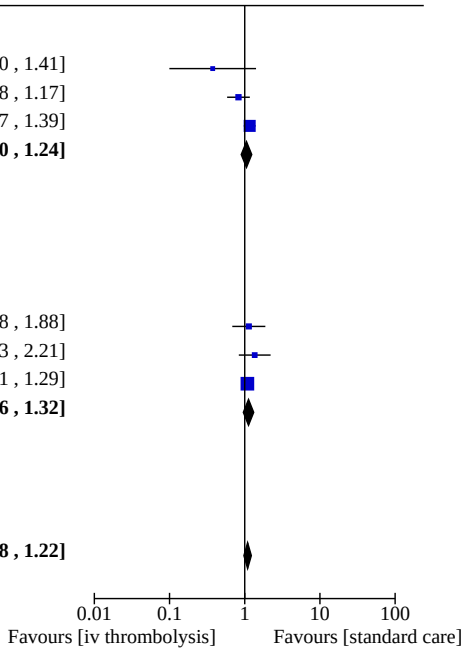
Analysis 4.4. Comparison 4: Subgroup analyses for good functional outcome after intravenous thrombolytic treatment, Outcome 4: Findings on imaging

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.4.1 Large vessel occlusion present						
EXTEND	21	52	17	53	8.4%	1.26 [0.75 , 2.10]
THAWS	9	13	4	10	2.3%	1.73 [0.75 , 4.01]
WAKE-UP	21	48	13	37	7.4%	1.25 [0.72 , 2.14]
Subtotal (95% CI)		**113**		**100**	**18.1%**	**1.31 [0.93 , 1.85]**
Total events:	51		34			
Heterogeneity: Chi² = 0.48, df = 2 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.57 (P = 0.12)						
4.4.2 Large vessel occlusion absent						
EXTEND	15	21	13	20	6.7%	1.10 [0.72 , 1.67]
THAWS	28	40	20	26	12.1%	0.91 [0.68 , 1.22]
WAKE-UP	143	172	129	180	63.1%	1.16 [1.04 , 1.30]
Subtotal (95% CI)		**233**		**226**	**81.9%**	**1.12 [1.01 , 1.24]**
Total events:	186		162			
Heterogeneity: Chi² = 2.32, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 2.12 (P = 0.03)						
Total (95% CI)		**346**		**326**	**100.0%**	**1.15 [1.04 , 1.28]**
Total events:	237		196			
Heterogeneity: Chi² = 3.67, df = 5 (P = 0.60); I² = 0%						
Test for overall effect: Z = 2.63 (P = 0.008)						
Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%						



Analysis 4.5. Comparison 4: Subgroup analyses for good functional outcome after intravenous thrombolytic treatment, Outcome 5: Time from first observation of symptoms to onset of treatment

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.5.1 <= 3 hours						
ECASS-4	2	8	4	6	2.4%	0.38 [0.10 , 1.41]
THAWS	17	25	14	17	8.8%	0.83 [0.58 , 1.17]
WAKE-UP	81	105	59	89	33.8%	1.16 [0.97 , 1.39]
Subtotal (95% CI)		**138**		**112**	**45.0%**	**1.06 [0.90 , 1.24]**
Total events:	100		77			
Heterogeneity: Chi² = 5.37, df = 2 (P = 0.07); I² = 63%						
Test for overall effect: Z = 0.65 (P = 0.51)						
4.5.2 > 3 hours						
ECASS-4	17	34	15	34	7.9%	1.13 [0.68 , 1.88]
THAWS	20	28	10	19	6.3%	1.36 [0.83 , 2.21]
WAKE-UP	80	112	81	123	40.8%	1.08 [0.91 , 1.29]
Subtotal (95% CI)		**174**		**176**	**55.0%**	**1.12 [0.96 , 1.32]**
Total events:	117		106			
Heterogeneity: Chi² = 0.74, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.44 (P = 0.15)						
Total (95% CI)		**312**		**288**	**100.0%**	**1.09 [0.98 , 1.22]**
Total events:	217		183			
Heterogeneity: Chi² = 6.25, df = 5 (P = 0.28); I² = 20%						
Test for overall effect: Z = 1.53 (P = 0.13)						
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%						



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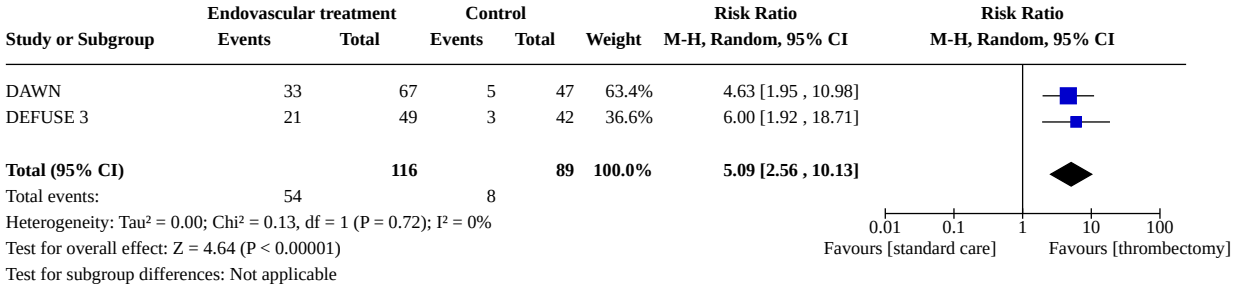
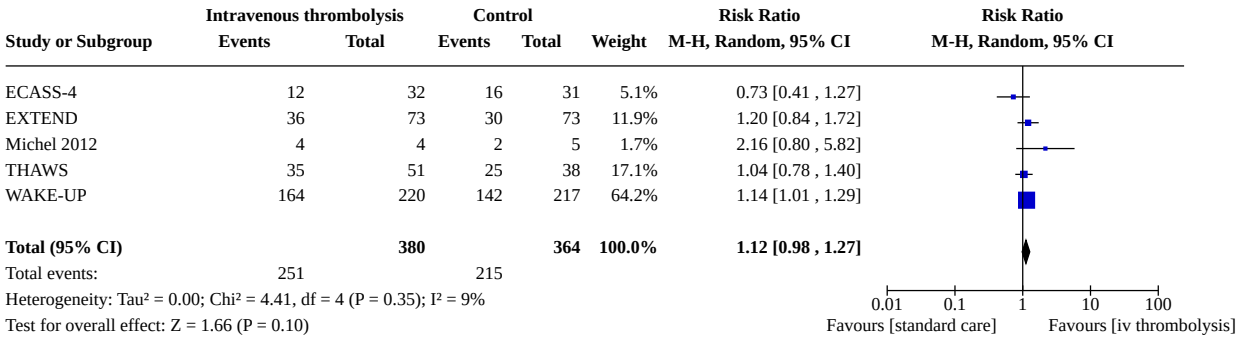
Comparison 5. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Endovascular treatment (random-effects model)	2	205	Risk Ratio (M-H, Random, 95% CI)	5.09 [2.56, 10.13]
5.2 Intravenous thrombolysis (random-effects model)	5	744	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.98, 1.27]

Analysis 5.1. Comparison 5: Sensitivity analysis, Outcome 1: Endovascular treatment (random-effects model)



Analysis 5.2. Comparison 5: Sensitivity analysis, Outcome 2: Intravenous thrombolysis (random-effects model)



APPENDICES

Appendix 1. CENTRAL search strategy

IDSearchHits
#1MeSH descriptor: [Cerebrovascular Disorders] this term only1391
#2MeSH descriptor: [Basal Ganglia Cerebrovascular Disease] this term only11
#3MeSH descriptor: [Brain Ischemia] this term only1466
#4MeSH descriptor: [Brain Infarction] explode all trees1061
#5MeSH descriptor: [Hypoxia-Ischemia, Brain] this term only177
#6MeSH descriptor: [Carotid Artery Diseases] this term only454
#7MeSH descriptor: [Carotid Artery Thrombosis] this term only18
#8MeSH descriptor: [Carotid Artery, Internal, Dissection] this term only5

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#9MeSH descriptor: [Intracranial Arterial Diseases] this term only10
#10MeSH descriptor: [Cerebral Arterial Diseases] explode all trees195
#11MeSH descriptor: [Infarction, Anterior Cerebral Artery] this term only6
#12MeSH descriptor: [Infarction, Middle Cerebral Artery] this term only129
#13MeSH descriptor: [Infarction, Posterior Cerebral Artery] this term only4
#14MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees292
#15MeSH descriptor: [Stroke] explode all trees8034
#16MeSH descriptor: [Vertebral Artery Dissection] this term only6
#17(isch*emi* near/6 (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva or attack*)):ti,ab,kw (Word variations have been searched)10139
#18((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,kw (Word variations have been searched)11475
#19{OR #1-#18}22941
#20MeSH descriptor: [Wakefulness] this term only933
#21MeSH descriptor: [Sleep] this term only3562
#22(("wake up" or "wake-up" or "wakes up" or "wakes-up")):ti,ab,kw (Word variations have been searched)441
#23((waking* or awake* or awoke)):ti,ab,kw (Word variations have been searched)5784
#24((during near/5 sleep*)):ti,ab,kw (Word variations have been searched)3240
#25((whil* near/5 (sleep* or asleep))):ti,ab,kw (Word variations have been searched)592
#26(((unknown or unclear or uncertain or indefinite or "not known") near/10 onset)):ti,ab,kw (Word variations have been searched)185
#27{or #20-#26}11631
#28MeSH descriptor: [Thrombolytic Therapy] this term only1584
#29MeSH descriptor: [Fibrinolytic Agents] this term only2084
#30MeSH descriptor: [Fibrinolysin] this term only133
#31MeSH descriptor: [Plasminogen] this term only220
#32MeSH descriptor: [Tissue Plasminogen Activator] this term only1553
#33MeSH descriptor: [Plasminogen Activators] explode all trees2436
#34MeSH descriptor: [Streptokinase] explode all trees794
#35MeSH descriptor: [Fibrinolysis] this term only969
#36((thromboly* or fibrinoly* or recanalis* or recanaliz*)):ti,ab,kw (Word variations have been searched)9943
#37(((clot* or thrombus) near/5 (lyse or lysis or dissolve* or dissolution or bust*))):ti,ab,kw (Word variations have been searched)1347
#38((tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse)):ti,ab,kw (Word variations have been searched)5810
#39((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,kw (Word variations have been searched)2599
#40MeSH descriptor: [Radiography, Interventional] this term only284
#41MeSH descriptor: [Radiology, Interventional] this term only34
#42MeSH descriptor: [Catheterization] this term only1563
#43MeSH descriptor: [Angioplasty] this term only275
#44MeSH descriptor: [Angioplasty, Balloon] this term only556
#45MeSH descriptor: [Angioplasty, Balloon, Laser-Assisted] this term only26
#46MeSH descriptor: [Angioplasty, Laser] this term only25
#47MeSH descriptor: [Catheter Ablation] this term only1356
#48MeSH descriptor: [Atherectomy] this term only25
#49MeSH descriptor: [Stents] this term only2838
#50MeSH descriptor: [Mechanical Thrombolysis] this term only34
#51MeSH descriptor: [Thrombectomy] explode all trees243
#52MeSH descriptor: [Embolectomy] this term only10
#53MeSH descriptor: [Blood Vessel Prosthesis] this term only440
#54MeSH descriptor: [Blood Vessel Prosthesis Implantation] this term only439
#55MeSH descriptor: [Cerebral Revascularization] this term only56
#56MeSH descriptor: [Reperfusion] this term only97
#57MeSH descriptor: [Dilatation] this term only395
#58((interventional near/3 (radiolog* or radiograph* or neuroradiolog*))):ti,ab,kw (Word variations have been searched)818
#59((angioplast* or stent*)):ti,ab,kw (Word variations have been searched)15680
#60((thrombectomy or embolectomy or atherect*)):ti,ab,kw (Word variations have been searched)1414
#61((thromboaspiration or arterial next recanali*ation)):ti,ab,kw (Word variations have been searched)47
#62(((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,kw (Word variations have been searched)580
#63(((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,kw (Word variations have been searched)629

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#64(((retrieval or extraction) near/5 device*)):ti,ab,kw (Word variations have been searched)100
#65((endoluminal next repair*)):ti,ab,kw (Word variations have been searched)2
#66((blood vessel near/5 (prosthesis or implantat*))):ti,ab,kw (Word variations have been searched)806
#67(((merci or concentric) next retriever)):ti,ab,kw (Word variations have been searched)19
#68((endovascular next snare* or neuronet or microsnare or "X-ciser" or angiojet)):ti,ab,kw (Word variations have been searched)21
#69MeSH descriptor: [Dilatation] this term only395
#70MeSH descriptor: [Ultrasonic Therapy] this term only751
#71MeSH descriptor: [Ultrasonography] this term only4610
#72MeSH descriptor: [Ultrasonography, Doppler] explode all trees2839
#73MeSH descriptor: [Ultrasonography, Interventional] this term only1594
#74((ultrasound* or ultrasonic* or ultrasonogra* or sonograph* or insonation)):ti,ab,kw (Word variations have been searched)29028
#75(((transcranial near/5 doppler) or TCD or TCCD)):ti,ab,kw (Word variations have been searched)1200
#76((sonothrombolysis or sonothromboly* or sonolys* or sonothrombotripsy or thrombotripsy)):ti,ab,kw (Word variations have been searched)115
#77{or #28-#76}60356
#78#19 AND #27 AND #7772

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$)).tw.
17. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
18. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).nm.
19. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or amediplase or monteplase or nasaruplase or silteplase).tw.
20. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or amediplase or monteplase or nasaruplase or silteplase).nm.
21. radiography, interventional/ or radiology, interventional/
22. catheterization/ or angioplasty/ or angioplasty, balloon/ or angioplasty, balloon, laser-assisted/ or angioplasty, laser/ or atherectomy/ or catheter ablation/
23. Stents/
24. mechanical thrombolysis/ or thrombectomy/ or embolectomy/
25. blood vessel prosthesis/ or blood vessel prosthesis implantation/
26. cerebral revascularization/ or reperfusion/ or dilatation/
27. (interventional adj3 (radiolog$ or radiograph$ or neuroradiolog$)).tw.
28. (angioplast$ or stent$).tw.
29. (thrombectomy or embolectomy or atherect$).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.

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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$.tw.
35. endoluminal repair$.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$)).tw.
18. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
19. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or amediplase or monteplase or nasaruplase or silteplase).tw.
20. interventional radiology/ or endovascular surgery/
21. percutaneous transluminal angioplasty/ or angioplasty/ or laser angioplasty/ or catheterization/ or catheter ablation/ or balloon dilatation/ or exp atherectomy/
22. Stents/
23. thrombectomy/ or exp percutaneous thrombectomy/ or embolectomy/
24. artery prosthesis/
25. cerebral revascularization/ or reperfusion/ or artery dilatation/ or recanalization/
26. (interventional adj3 (radiolog$ 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 fragmentation 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$)).tw.
32. ((retrieval or extraction) adj5 device$).tw.
33. endoluminal repair$.tw.
34. ((blood vessel or artery) adj5 (prosthesis or implantat$)).tw.
35. ((merci or concentric) adj retriever).tw.

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36. (endovascular snare$ or neuronet or microsnare or X-ciser or angiojet).tw.
37. ultrasonics/ or ultrasonic therapy/ or ultrasonography/ or exp ultrasonography, doppler/ or ultrasonography, interventional/
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: wake-up AND stroke OR awakening AND stroke

(http://apps.who.int/trialsearch/)

Appendix 6. Stroke Trials Registry search strategy

Key words: wake

WHAT'S NEW

Date	Event	Description
7 April 2021	New search has been performed	This review has been updated with searches performed on 24 May 2021. It now includes six new trials for a total of seven trials involving 980 participants. The title of the review has been changed from 'Recanalisation therapies for wake-up stroke' to 'Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic wake-up stroke'.
7 April 2021	New citation required and conclusions have changed	We updated and changed the conclusions from earlier published versions of the review.

HISTORY

Protocol first published: Issue 3, 2014
Review first published: Issue 8, 2018

CONTRIBUTIONS OF AUTHORS

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

All authors drafted the manuscript and approved its content.

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DECLARATIONS OF INTEREST

Melinda Roaldsen: *Declaring financial interests, Other:* Trial Manager for TWIST (Tenecteplase in Wake-up Ischaemic Stroke Trial), University Hospital of North Norway (funds received by author). *Declaring non-financial/other interests, Published opinions in medical journals, the public press, broadcast and social media relevant to the interventions in the work*: First author on the following article: Roaldsen MB, Lindekleiv H, Eltoft A, Jusufovic M, et al. Tenecteplase in wake-up ischaemic stroke trial (TWIST): Protocol for a randomised-controlled trial, 14 January 2021, International Journal of Stroke, TWIST/University Hospital of North Norway. The main source of funding for the ongoing TWIST study is Norwegian Government Funding from the Clinical Therapy Research in the Specialist Health Services Research Programme. Additional grants are from the Swiss Heart Foundation, the British Heart Foundation, and the Norwegian National Association for Public Health. The cost of tenecteplase is also covered by an unconditional grant from Boehringer Ingelheim Norway KS. The study is an investigator- and academically initiated study. The funders of the study had no role in the study design or data collection.

Haakon Lindekleiv: none known.

Ellisiv Mathiesen: *Declaring non-financial/other interests, Other:* Co-ordinating Investigator of the Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST), University Hospital of North Norway, Tromsø, Norway. A protocol article about the rationale for and design of TWIST has been published in the International Journal of Stroke. TWIST is an ongoing trial and therefore not included in the current analyses, but the trial is mentioned in the article. The main funding source for TWIST is from the Norwegian Clinical Therapy Research in the Specialist Health Services Research Programme (KLINBEFORSK; funded by the Norwegian Ministry of Health and Care Services). The trial has also received funding from the Norrwegian National Association for Public Health, the British Heart Foundation, and the Swiss Heart Foundation. The cost of the investigational medicinal product used in the trial is covered by Boehringer Ingelheim GmbH.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We were unable to procure data for the following planned secondary outcomes:

- quality of life at the end of follow-up;
- neurological status at seven to 14 days and at the end of follow-up.

We split the statistical analysis for studies where participants received intravenous thrombolysis and for studies where participants received endovascular thrombectomy. We did this after conferring with and receiving advice from the Cochrane Stroke Group.

The title of this review has changed from 'Recanalisation therapies for wake-up stroke' to 'Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic wake-up stroke'. This change of title has no implications for the original scope of the review, and is simply a change in terminology.

INDEX TERMS

Medical Subject Headings (MeSH)

Fibrinolytic Agents [therapeutic use]; Intracranial Hemorrhages; *Ischemic Stroke; *Stroke [drug therapy]; Thrombectomy

MeSH check words

Humans

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