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Aspects on Recanalisation Therapies for Acute Ischaemic Stroke

Long-term survival after thrombolytic treatment with alteplase, endovascular thrombectomy for acute ischaemic stroke and recanalisation therapies for wake-up stroke

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SUMMARY

Stroke is a leading cause of death and disability worldwide. Approximately 85% of strokes are ischaemic strokes caused by blockage of a brain artery. From having limited acute treatment modalities, intravenous thrombolytic treatment and endovascular interventions have revolutionised acute ischaemic stroke treatment during the last 25 years. Thrombolysis means to dissolve (lysis) the blood clot (thrombus), while thrombectomy means mechanical removal of the blood clot. Thrombolysis is most effective when given as early as possible within 4.5 hours after symptom onset. Thrombectomy has been shown to benefit patients with blood clot in a large brain artery if given within 6 hours and in selected cases up until 24 hours after symptom onset. These acute treatment modalities are today offered to patients who arrive at the hospital within the given time limits.

Several studies have found that thrombolysis given within 4.5 hours after stroke onset improves functional outcome in acute ischaemic stroke patients after 3 to 6 months, but not survival. Knowledge on the effect on long-term survival is scarce. We assessed the effect of thrombolysis on long-term survival up to 3 years after ischaemic stroke in an international multicentre, randomised controlled trial. We found a non-significant lower death rate after 3 years in patients treated with thrombolysis. Mortality was higher in the thrombolysis group in the first seven days mainly due to intracerebral haemorrhage, while patients who survived the first week had significantly higher long-term survival after 3 years.

In a systematic review and meta-analysis, we assessed the safety and efficacy of endovascular thrombectomy and/or intra-arterial thrombolysis in patients with acute ischaemic stroke. We found that treatment with thrombectomy and intra-arterial thrombolysis increased the chance of achieving a good functional outcome. Such treatment also reduced the risk of death at the end of follow-up without increasing the risk of symptomatic intracranial haemorrhage.

In about 20% of ischaemic stroke patients, the stroke occurs during sleep (wake-up stroke). To assess the safety and efficacy of recanalisation therapies in ischaemic wake-up stroke patients, we conducted a systematic review and meta-analysis of endovascular thrombectomy and thrombolysis in patients with wake-up stroke. We identified seven eligible trials involving a total of 980 participants. The results showed that recanalisation therapies can improve functional outcome and survival in selected people with wake-up stroke.

We are currently conducting an international multicenter randomised controlled trial of thrombolytic treatment with tenecteplase in patients with ischaemic wake-up stroke aimed at testing whether thrombolytic treatment with tenecteplase given within 4.5 hours of wake-up can improve functional outcome at 3 months. The design and methods for this trial are presented in the thesis. If thrombolytic treatment is shown to benefit wake-up stroke patients, this can lead to improved stroke treatment for a large proportion of stroke patients.

SAMMENDRAG

Hjerneslag er en av de vanligste årsakene til død og sykelighet over hele verden. Omtrent 85% av alle hjerneslag er iskemiske hjerneslag som oppstår som følge av at en blodåre i hjernen går tett, som regel pga. blodpropp. Mens akutte behandlingsmetoder tidligere var svært begrenset, har nye metoder som intravenøs trombolytisk behandling og endovaskulær trombektomi revolusjonert behandlingen av akutt iskemisk hjerneslag i løpet av de siste 25 årene. Trombolyse betyr å løse opp (lysis) blodproppen (thrombus), mens trombektomi betyr å fjerne blodproppen mekanisk. Trombolyse har god effekt forutsatt at det blir gitt så raskt som mulig innen 4,5 timer etter symptomstart. Trombektomi er vist å ha god effekt hos pasienter med blodpropp i store blodårer forutsatt at behandlingen blir gjort innen 6 timer etter symptomstart og i utvalgte tilfeller opptil 24 timer etter symptomstart. Disse behandlingsmetodene tilbys i dag til pasienter med akutt hjerneslag forutsatt at pasienten kommer tidlig nok til behandling.

Flere studier har funnet at trombolyse som blir gitt innen 4,5 timer fra symptomstart forbedrer funksjonelt utkomme etter 3 og 6 måneders oppfølging hos pasienter med akutt iskemisk hjerneslag, men uten sikker effekt på overlevelse. Det finnes lite kunnskap om effekten på langtidsoverlevelse. Vi undersøkte effekten av trombolyse på langtidsoverlevelse opp til 3 år etter iskemisk hjerneslag i en stor internasjonal, multisenter, randomisert kontrollert studie. Vi fant en ikke-signifikant lavere dødelighet etter 3 år hos pasienter behandlet med trombolyse. I gruppen som ble behandlet med trombolyse var mortaliteten høyere de første syv dagene som følge av økt forekomst av hjerneblødning, mens de som overlevde den første uken hadde signifikant høyere langtidsoverlevelse etter 3 år.

I en systematisk litteraturgjennomgang og metaanalyse vurderte vi sikkerhet og effekt av endovaskulær trombektomi og/eller intraarteriell trombolyse hos pasienter med akutt iskemisk hjerneslag. Vi fant at behandling med trombektomi og intraarteriell trombolyse økte sjansen for å få et godt funksjonelt utkomme. Behandling med trombektomi reduserte også risikoen for død ved slutten av oppfølgingsfasen og medførte ingen økt risiko for symptomatisk hjerneblødning.

Ca. 20% av alle iskemiske hjerneslag oppstår under søvn (oppvåkningshjerneslag). For å vurdere sikkerheten og effekten av behandlingsmetoder for å gjenopprette blodsirkulasjonen i den tette blodåren hos pasienter med oppvåkningshjerneslag, utførte vi en systematisk litteraturgjennomgang og metaanalyse av endovaskulær trombektomi og intravenøs trombolyse hos pasienter med oppvåkningshjerneslag. Vi identifiserte syv aktuelle studier med totalt 980 deltakere. Resultatene viste at intravenøs trombolyse og trombektomi kan forbedre funksjonelt utkomme og overlevelse hos utvalgte pasienter med oppvåkningshjerneslag.

Vi gjennomfører nå en internasjonal randomisert, kontrollert multisenterstudie av effekten av trombolytisk behandling med tenekteplase hos pasienter med iskemisk oppvåkningshjerneslag. Målet med studien er å undersøke om trombolytisk behandling med tenekteplase innen 4,5

timer fra oppvåkning kan bedre funksjonelt utkomme tre måneder etter hjerneslaget. Metode og design for denne studien presenteres i avhandlingen. Hvis trombolytisk behandling med tenekteplase er effektivt, vil dette kunne bedre det akutte behandlingstilbudet til en større gruppe hjerneslagspasienter.

LIST OF PAPERS

I. Berge E, Cohen G, Roaldsen MB, Lundström E, Isaksson E, Rudberg A-S, Slot KB, Forbes J, Smith J, Drever J, Wardlaw JM, Lindley RI, Sandercock PAG, Whiteley WN. Effects of alteplase on survival after ischaemic stroke (IST-3): 3-year follow-up of a randomised, controlled, open-label trial. *Lancet Neurology*. 2016; 15(10): 1028-1034

II. Roaldsen MB, Jusufovic M, Berge E, Lindekleiv H. Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2021; 6(6): CD007574

III. Roaldsen MB, Lindekleiv H, Mathiesen EB. Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic wake-up stroke. Submitted to *Cochrane Database of Systematic Reviews* June 6, 2021 and re-submitted September 7, 2021

IV. Roaldsen MB, Lindekleiv H, Eltoft A, Jusufovic M, Søyland M-H, Petersson J, Indredavik B, Tveiten A, Putaala J, Christensen H, Kõrv J, Jatuzis D, Engelter ST, de Marchis GM, Wilsgaard T, Werring DJ, Robinson T, Mathiesen EB, Berge E. Tenecteplase in wake-up ischaemic stroke trial (TWIST): Protocol for a randomised controlled trial. *International Journal of Stroke*. January 14, 2021. doi: 10.1177/1747493020984073 (published online ahead of print)

Abbreviations

ASA	American Stroke Association
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTP	Computed Tomography Perfusion
DWI	Diffusion Weighted Imaging
FLAIR	Fluid Attenuated Inversion Recovery
ICH	Intracerebral haemorrhage
IST-3	The Third International Stroke Trial
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NCCT	Non-contrast Computed Tomography
NIHSS	National Institutes of Health Stroke Scale
NINDS	The National Institute of Neurological Disorders and Stroke
RR	Risk ratio
TWIST	Tenecteplase in Wake-up Ischaemic Stroke Trial

1. INTRODUCTION

1.1 Definition and epidemiology of stroke

Stroke is defined as “rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin”.[1] A continuous blood supply to the brain is essential for normal brain function, as brain tissue damage and death can arise only minutes after blood flow is interrupted.[2]

Stroke is a leading cause of death and preventable disability worldwide.[3, 4] Globally there are over 13 million new stroke cases annually.[5] In Norway the annual incidence rate is estimated to approximately 10 000 patients for first-ever stroke.[6] Although mortality due to stroke has decreased the last 30 years,[3] the impact of ischaemic stroke on health care services is expected to increase because of an ageing population.[7, 8]

The most important modifiable risk factors for stroke include hypertension, cigarette smoking, atrial fibrillation, dyslipidaemia, diet, diabetes mellitus, obesity, physical inactivity, cardiac disease, and alcohol.[9, 10] Non-modifiable risk factors include age, sex, ethnicity, low birth weight and hereditary factors.[10] Comorbidity and the simultaneous occurrence of several risk factors is important in all major subtypes of ischaemic stroke.[11, 12]

1.2 Pathophysiology and classification of ischaemic stroke

Stroke is caused by the disruption of blood circulation to parts of the brain, resulting in brain tissue damage due to deprivation of oxygen and nutrients. Approximately 85% of strokes are ischaemic strokes caused by blockage of an artery (Figure 1). The remaining 15% of strokes are constituted of either intracerebral or subarachnoid haemorrhage.[13]

Figure 1 Illustration of ischaemic stroke (left) and haemorrhagic stroke (right)

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Brain ischaemia because of arterial blockage can arise because of several pathophysiological mechanisms. The most common is atherosclerosis,[14] which is a chronic disease developing slowly and progressing during the entire lifespan and in an individual rate.[15] It is characterized by chronic inflammatory changes with accumulation of low-density lipoprotein (LDL) cholesterol, small muscle cells, calcification and fibrous tissue in the vessel wall.[16] Disruption of the atherosclerotic lesions may cause thrombus formation.[17] Rare causes for ischaemic stroke are arterial dissection, vasculitis, coagulopathy, and hypoperfusion due to systemic hypotension or stenosis.[18]

There are many different stroke subtype classification systems based on localisation, clinical manifestations, causative factors or a combination of these.[19-23] A major challenge in stroke studies is the lack of a gold standard for classification, and it may often be debatable whether a stroke occurred due to embolism, atherothrombosis or hemodynamic changes. The Trial of Org 10172 in Acute Stroke Treatment (TOAST)[21] criteria have received criticism regarding reliability and validity,[24] but remains the most used classification system for stroke for clinicians and researchers.[25] TOAST classifies ischemic strokes in five etiological categories:

1. Large artery atherosclerosis
2. Cardioembolism
3. Small-vessel occlusion
4. Stroke of other determined causes
5. Stroke of undetermined causes

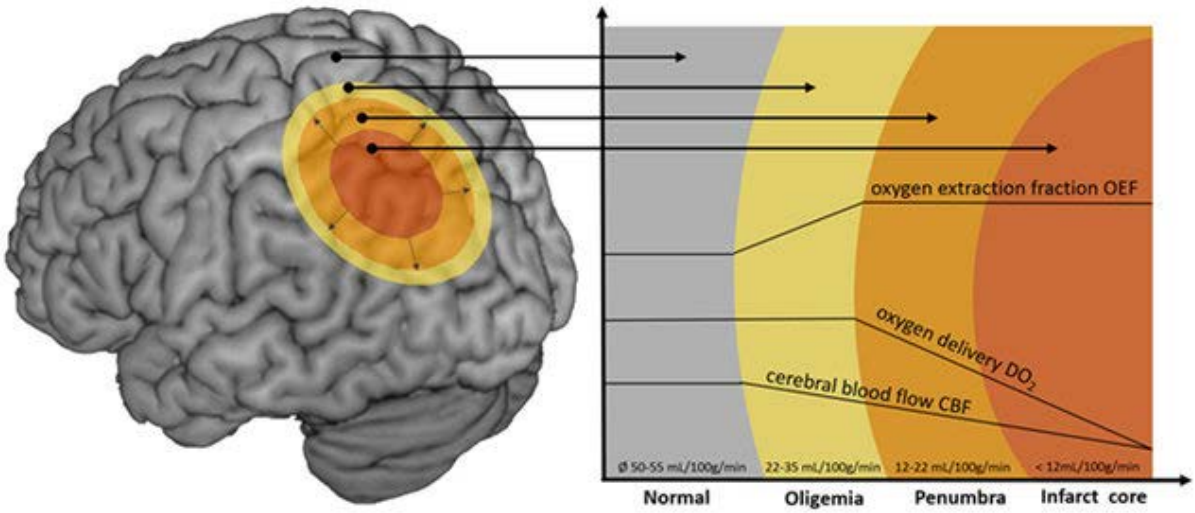
Atherosclerosis is the main pathophysiological mechanism in large vessel disease. Occlusion of the artery may be caused by local atherothrombosis in an intracranial artery or by artery-to-artery emboli from precerebral to intracranial arteries.[26] Large vessel disease account for approximately 8-15% of all ischaemic stroke.[27] In small-vessel disease, lacunar infarcts are caused by occlusion of small penetrating end-arteries supplying deep brain structures and are smaller than 15 mm.[28] They account for approximately 20-30% of all ischaemic stroke.[26] Lacunar infarcts are associated with hypertension and diabetes mellitus.[29] Cardioembolic strokes arise because of an arterial occlusion due to an embolus of cardiac origin.[30] They account for approximately 20-30 % of all ischaemic stroke.[26] Cardiac emboli tend to often cause multiple infarct in both single and multiple areas and recurrence of stroke.[31, 32] Stroke from undetermined causes are often called cryptogenic stroke and constitute approximately 20-30% of all ischemic stroke.[33]

1.3 The ischaemic penumbra

The penumbra is an area of ischaemic, but still viable brain tissue surrounding the core of a cerebral infarction (Figure 2). The penumbra is assumed to be salvageable if blood flow can be rapidly restored.

Normal values of cerebral blood flow are about 50 ml/(100 g min)[34] with lower levels in white matter and higher levels in grey matter.[35] Blood flow reduction causes metabolic disturbances at certain blood flow thresholds leading to depleted adenosine triphosphate levels in the ischaemic core and consequently cell death.[36] The penumbra, or tissue-at-risk, has a more gradient reduction of adenosine triphosphate levels between normal tissue and the ischaemic core and can survive for a longer amount of time.[37] Recanalisation of the occluded vessel and regaining reperfusion can reduce the final size of the infarct. To salvage the penumbra is one of the main goals of acute ischaemic stroke therapies.[37]

Figure 2 Illustration of the Penumbra Concept



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1.4 Imaging in acute ischaemic stroke

Non-contrast computed tomography (NCCT) can identify haemorrhagic stroke and can therefore distinguish between ischaemic and hemorrhagic stroke.[38] It is the most rapid and available imaging modality and therefore the preferred choice in the acute setting. Computed tomography angiography (CTA) is used for rapid assessment of large vessel occlusion.[38] CTA can also provide insight into collaterals in patients with ischaemic stroke.[39] Computed

tomography perfusion (CTP) improves diagnostic accuracy of ischaemic stroke by providing penumbra imaging.[40] CTP can be used to measure: cerebral blood volume, cerebral blood flow, mean transit time and time to peak enhancement. The advantages of CT perfusion over magnetic resonance imaging (MRI) imaging is that it is more readily available in the acute setting and can be performed quickly after a non-contrast CT.[41] CT penumbral methods are being increasingly applied in clinical practice.[40]

Another imaging modality being increasingly used in clinical stroke diagnostics is magnetic resonance imaging.[42] In the acute stroke setting, diffusion weighted imaging (DWI) scans are particularly valuable. DWI is designed to detect the random movement of water protons. Acute ischaemic stroke lesions on DWI are thought to represent alterations to water diffusion and can be visualised within minutes of onset.[43] Fluid attenuation inversion recovery (FLAIR) is a different sequence and cannot be identified until after a few hours from onset when stroke vasogenic oedema gradually appear.[44] Findings suggestive of ischaemic stroke on DWI, but absence of such findings on FLAIR, also called DWI/FLAIR mismatch, may therefore be used to identify patients with a short time from ischaemic stroke onset. MR perfusion imaging is comparable to CT perfusion imaging.[45] Areas with abnormal imaging can identify both dead tissue and tissue at risk. By combining diffusion and perfusion imaging tissue at risk, also called penumbra, can be identified. Penumbra imaging, either by CT or MR perfusion, can therefore be used to quantify the amount of salvageable brain tissue in patients with both known and unknown symptom onset.

1.5 Outcome assessment in clinical stroke trials

The outcome of stroke can be classified according to vital status, working capacity (employment), functional outcome, quality of life, health economics and other relevant aspects. The modified Rankin Scale (mRS)[46] is the most commonly used scale for assessment of functional outcome after stroke, where functional status is classified from 0-6 as no disability (mRS=0) to death (mRS=6) (appendix I). mRS scores are often dichotomised as 0-1 (excellent outcome) vs 2-6 or 0-2 (good functional outcome) vs 3-6.

1.6 Recanalisation therapies for acute ischaemic stroke

Recanalisation therapies include intravenous and intra-arterial thrombolytic treatment and endovascular mechanical thrombectomy, and the implementation of these methods in everyday clinical practice has led to ischaemic stroke now being recognised as a highly acute condition. It has been quantified that a patient loses approximately 1.9 million neurons each minute during an untreated stroke, prompting an urgent need for an effective chain of health care services so that the correct diagnosis can be established and appropriate treatment initiated as soon as possible (time is brain).[2]

1.6.1 Thrombolytic treatment

Thrombolysis means to dissolve (lysis) the blood clot (thrombus). That certain substances could active the fibrinolytic system was discovered in the 1930s.[47] Thrombolytic drugs were used to treat acute ischaemic stroke for the first time in 1958. However, there was no way to select the appropriate patients for treatment of ischaemic stroke before CT was introduced in the 1970s.[47] Thrombolytic drugs are derived from naturally occurring plasminogen activators which dissolve the thrombus as part of the natural clotting cascade. These plasminogen activators act by binding to fibrin protein threads of the thrombus and converting plasminogen into plasmin,[48-50] thus initiating local fibrinolysis. Streptokinase bind with free circulating plasminogen or plasmin to form a complex that can convert additional plasminogen to plasmin.[51] Some thrombolytic drugs are extracted from biological samples (urokinase, desmoteplase) and others are manufactured (alteplase, pro-urokinase, tenecteplase).[52]

1.6.2 Intravenous thrombolytic treatment with alteplase (rt-PA)

Thrombolytic agents can be administered intravenously or intra-arterially. Alteplase is the only approved drug for intravenous thrombolytic treatment for acute ischaemic stroke.[53] Alteplase is a tissue plasminogen activator produced by DNA recombinant technology,[48] often referred to as recombinant tissue plasminogen activator (rt-PA). It is administrated intravenously with an initial 10% bolus dose over 1 minute followed by an 1-hour infusion of 0.9 mg/kg, (maximum 90 mg). In 1995, results from the National Institute of Neurological Disorders and Stroke Study (NINDS),[54] a randomised controlled trial with 624 patients, showed that treatment with intravenous alteplase within 3 hours from stroke onset improved clinical outcome at 3 months despite an increased incidence of intracerebral haemorrhage. The European Cooperative Acute Stroke Study (ECASS),[55] was published in the same year as NINDS, and the later Second European-Australasian Acute Stroke Study (ECASS II)[56] (n=623 and 800, respectively) failed to show efficacy of treatment with alteplase 1.1 mg /kg within 3 hours of

symptom onset. The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke trial showed a positive outcome despite a significant increase in the rate of symptomatic intracranial haemorrhage in 61 patients randomised to alteplase or placebo within 3 hours of symptom onset.[57] While alteplase was licensed for treatment of acute stroke in the USA in 1996 and in Canada in 1998, the divergent results from clinical trials led to approval of alteplase in the European Union in 2002 on two conditions: the initiation of an observational safety study, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)[58] and a new randomised trial with an extended therapeutic window beyond 3 hours, ECASS III.[59] SITS-MOST confirmed that treatment with alteplase within 3 hours is safe and effective in routine clinical practice.[60] ECASS III[59] tested the efficacy and safety of alteplase administrated between 3 and 4.5 hours after the onset of stroke in 821 patients and showed that treatment with alteplase significantly improved clinical outcome at 3 months. The Third International Stroke Trial (IST-3) tested alteplase in acute ischaemic stroke patients within 6 hours of symptom in 3035 patients and found no significant improvement in functional outcome, defined as an Oxford Handicap Score (OHS) of 0-2 at 6 months (Appendix II).[61] A secondary ordinal analysis which was adjusted for age, National Institutes of Health Stroke Scale (NIHSS), delay, and presence or absence of visible acute ischaemic change on baseline scan, and with prespecified OHS levels where 4, 5, and 6 were grouped and 0, 1, 2, 3 remained discrete, the analysis showed a significant shift in OHS, indicating benefit of thrombolysis common odds ratio (OR 1.27, 95% CI 1.10 to 1.47, p = 0.001).[61] A meta-analysis of nine randomised trials with individual participant data from 6756 patients showed a favourable outcome for 259 (32.9%) of 787 patients who received alteplase versus 176 (23.1%) of 762 who received control (OR 1.75, 95% CI 1.35 to 2.27).[62] Additional pooled analysis of these 6756 patients from 9 randomised trials showed that treatment with alteplase was beneficial up to 4.5 hours from stroke onset with a greater benefit with earlier treatment 55 patients per 1000 treated, (95% CI, 13 to 91).[63]

1.6.3 Intravenous thrombolytic treatment with streptokinase and desmoteplase

Randomised controlled trials of treatment with streptokinase has shown higher mortality in the treatment group and no difference in functional outcome between treatment with streptokinase and placebo.[64-66] Similarly, trials on desmoteplase have failed to prove consistent net benefit in acute ischaemic stroke.[67-71] Routine use of streptokinase and desmoteplase is therefore not recommended in acute ischaemic stroke.

1.6.4 Intravenous thrombolytic treatment with tenecteplase

Tenecteplase is a genetically engineered alteplase molecule with modification of three amino acid enzymatic sites produced to increase fibrin specificity and prolong its half-life. It has a 14-fold higher fibrin specificity than alteplase.[72] It is easier to administrate compared to alteplase, as it only requires one single bolus dose and does not need a continuous intravenous infusion after the bolus dose, as with alteplase. Tenecteplase has become the gold-standard for treatment of acute myocardial infarction after the publication of the Assessment of the Safety of a New Thrombolytic (ASSENT-2) trial in 1999 which randomised 16 949 patients with myocardial infarction to alteplase or tenecteplase.[73] ASSENT-2 found that tenecteplase was equivalent to alteplase in the treatment of acute myocardial infarction, but with lower risk of non-cerebral bleeding complications and easier administration.

Several randomised studies in patients with acute ischaemic stroke indicate that tenecteplase is associated with the same or better recanalisation rates and clinical outcomes compared to alteplase, and a similar or lower risk of intracerebral haemorrhage.[74-76] The TNK-Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke With Proven Occlusion trial (TEMPO-1) was a multicentre, prospective, not controlled, dose-escalation-safety and feasibility trial which showed that treatment with tenecteplase was feasible and seemed safe for minor stroke with intracranial occlusion.[77] Randomised controlled trials have found divergent results.[74-76, 78] Haley et al found no statistical differences in three month functional outcome between tenecteplase doses of 0.1, 0.25 and 0.4 mg/kg compared with alteplase 0.9 mg/kg in 112 patients.[74] The rate of symptomatic intracerebral haemorrhage was highest in the 0.4 mg/kg tenecteplase group. A randomised, phase 2B trial with 75 patients showed that tenecteplase was associated with significantly better reperfusion rates and clinical outcomes than alteplase in patients selected by CT perfusion.[76] The Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST) showed no difference between patients treated with alteplase and tenecteplase for the primary endpoint of percentage of salvaged CT perfusion-defined penumbra.[79] In the Norwegian Tenecteplase Stroke Trial (NOR-TEST), tenecteplase 0.4 mg/kg was compared to alteplase 0.9 mg/kg in 1107 patients with mostly mild strokes.[80] The trial showed that tenecteplase was as safe and effective, but not superior to alteplase as treatment for acute ischaemic stroke.[80] The Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke (EXTEND IA TNK) trial compared treatment with tenecteplase 0.25 mg/kg to alteplase 0.9 mg/kg before thrombectomy in 202 patients.[81] Tenecteplase before thrombectomy resulted in better functional outcome after 90 days than alteplase, (OR 1.7, 95% CI 1.0 to 2.8).[81]

In the 2019 update of the American Stroke Association (ASA) guidelines for the early management of acute ischemic stroke, tenecteplase is recommended as a potential alternative to alteplase in patients with minor neurological impairment and no major intracranial

occlusion.[38] The guidelines also suggested that it might be reasonable to choose tenecteplase over alteplase in patients eligible to undergo mechanical thrombectomy.[38]

1.6.5 Intra-arterial thrombolysis

Intra-arterial thrombolysis is a recanalisation technique injecting thrombolytic medication directly into the blocked artery causing the acute ischaemic stroke. Several randomised controlled trials have tested the safety and efficacy of intra-arterial local delivery of urokinase in acute ischaemic stroke.[82, 83] Despite an increased frequency of intracerebral haemorrhage, functional outcome was significantly improved at 90 days after treatment with intra-arterial urokinase compared to placebo within 6 hours of onset of acute ischaemic stroke.[83] It is currently used in some Asian countries,[84, 85] but not worldwide. This is because it has only been tested in a small number of randomised controlled trials comparing intravenous thrombolytic treatment as control[86] and because of possible side effects. It is therefore classified as having a low level of evidence in the ASA guidelines.[38]

1.6.6 Long-term outcome after thrombolytic treatment of acute ischaemic stroke

Studies have found that thrombolysis with alteplase improves functional outcome, but not survival in acute ischaemic stroke patients at 3 months to 18 months.[87] Few randomised controlled trials have performed long-term follow-up in their participants. Treatment which improves functional outcome after stroke could potentially lead to improved survival in the long run, for example because better motor function could lead to lower risk of thrombosis, infections as well as reduced fall risk.

1.6.7 Endovascular mechanical thrombectomy

Thrombectomy is a minimally invasive procedure for the endovascular, mechanical removal of the occluding arterial blood clot that has caused the acute ischemic stroke. The procedure is performed under guidance of digital subtraction angiography with the patient in conscious sedation or general anesthesia. It can be performed by 3 different methods: stent-retriever thrombectomy, direct thrombo-aspiration or a combined technique with use of stent retriever and concomitant thrombo-aspiration.

The first three randomised controlled trials on thrombectomy for acute ischaemic stroke published in 2013 were neutral.[88-90] In 2015, four randomised controlled trials presented positive results for endovascular thrombectomy in acute ischaemic stroke patients with

proximal arterial occlusions in the anterior circulation within 6 hours after symptom onset.[91-94] Two trials of endovascular thrombectomy have shown benefit of thrombectomy in an extended time window of up to 16 and 24 hours in selected patients with radiological indications of penumbra.[95,96] These results have been met with enthusiasm in the stroke community and have changed clinical practice guidelines.[38] However, the number of participants in each trial was relatively low (ranging from 16 to 656), and the efficacy and safety of these relatively new acute treatment modalities in different groups of ischaemic stroke patients have not been studied in detail.

1.7 Wake-up Stroke

Stroke of unknown onset describes a stroke where the patient is unaware or unable to state when the stroke symptoms started, and the stroke has not been witnessed by others. In the present thesis, stroke of unknown onset is used to describe unwitnessed strokes occurring during daytime as opposed to those occurring during sleep. A wake-up stroke is defined as a stroke that occurs when a person wakes up with newly acquired stroke symptoms that were not present before sleep. Wake-up strokes represent approximately 20% of all acute ischaemic strokes.[97-99] Studies have indicated that wake-up strokes differ from daytime unwitnessed stroke as they tend to have more severe acute stroke symptomatology.[100, 101]

Epidemiological studies have shown a circadian rhythm of acute ischaemic stroke.[102, 103] More ischaemic stroke patients are detected in the morning and early daytime hours with a gradual decrease throughout the day and night.[104] A large meta-analysis of 31 studies with a total of 11 816 strokes cases, showed a significant circadian variation in time of symptom onset with higher likelihood of onset in the morning hours (49% higher risk) and less likely during the night.[103] The same circadian variation has been seen in patients with acute myocardial infarction and sudden death and that could mean that there are some common denominators.[103]

The higher prevalence of stroke onset in the early morning hours is stipulated to be correlated to circadian variations of blood pressure levels.[105] There are also other factors such as occurrence of atrial fibrillation episodes and other haemostatic variations such as morning increase in platelet aggregation,[106] coagulation factors, fibrinolytic activity, plasma viscosity and haematocrit, and morning endothelial dysfunction.[104] Rapid eye movement sleep also seems to be associated with an increased risk.[107] Obstructive sleep apnea with short cessation of breathing during sleep is also observed to be more frequent in wake-up stroke patients.[108] It is also hypothesized that sleep might impact both the expression and perception of stroke symptoms by afflicted patients, including arousal because of the occurring stroke.[109, 110]

1.7.1 Recanalisation therapies for wake-up stroke

Because the time of stroke onset is unknown, wake-up stroke patients have been considered ineligible for thrombolytic treatment. However, if wake-up strokes occur close to awakening, as the circadian variation in stroke occurrence and cardiovascular risk factors may indicate,[104] this could mean that wake-up stroke patients may benefit from thrombolytic treatment. Results from observational studies have suggested that thrombolytic treatment was safe in wake-up stroke patients.[111-116] In recent years, four randomised controlled trials have tested the safety and efficacy of thrombolytic treatment in patients with stroke of unknown onset, including wake-up stroke.[117-120] These trials have shown diverging results, with a positive effect in favour of thrombolysis in two trials,[117, 120] while two were neutral.[118, 119] The number of participants of the trials were rather limited, ranging from 116 to 503 patients.

Two trials tested the safety and efficacy of endovascular thrombectomy in selected stroke patients in the extended time window from 6 hours up to 24 hours after stroke onset.[95, 96] Patients with wake-up stroke were included, but separate results for wake-up stroke have not been presented.

Studies on recanalisation therapies in wake-up stroke have used advanced imaging techniques to identify patients with high probability of short duration from stroke onset or with large ischaemic penumbra. MRI DWI/FLAIR mismatch technique was utilised in two trials,[117, 118] while assessments of CT or MR perfusion ischemic core and penumbral volumes were applied in others.[119] Whether advanced imaging is superior for selection of wake-up stroke patients who are likely to benefit from acute thrombolytic treatment compared to plain CT has not been tested in clinical randomised controlled trials.

1.8 Evidence based medicine

The term evidence based medicine may be defined as «the conscientious, explicit, judicious and reasonable use of modern, best evidence in making decisions about the care of individual patients».[121] Information on the effect of a particular treatment for a specific condition can be obtained by observational studies (case reports, case-control studies, and cohort studies), interventional trials (randomised controlled trials), and systematic synthesis of the existing evidence (systemic review and meta-analyses).

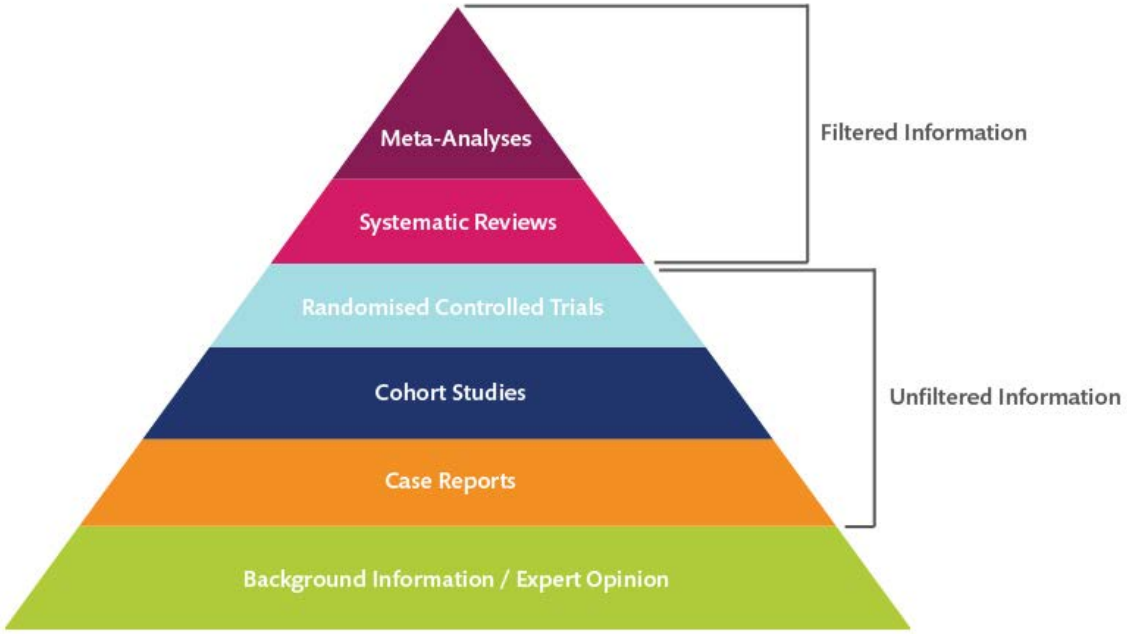
James Lind has historically been looked upon as the father of randomised controlled clinical trials. In 1755, he tested and found that citrus was an effective and safe treatment for scurvy in sailors aboard the HMS Salisbury. He randomly assigned some of the sailors to received liquid with citrus while some received liquid without citrus, and the sailors who received citrus became far better from their scurvy.[122] Randomised controlled trials are prospective studies that

measure the effectiveness of a new intervention or treatment and where a treatment is randomly allocated to participants of the trial.[123] The design is often placebo-controlled and double-blind where neither the treating physician nor the patient knows which treatment the patient receives. Randomised controlled trials continues to be the gold standard for studying causal relationships as randomisation minimises the risk of bias as no other study design can.

One of the most important achievements of evidence-based medicine have been the development of systematic reviews and meta-analyses.[124] A systematic review "attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question."[125] A systematic review adheres to specific methodology and often includes meta-analyses of aggregate data or individual participant data, where the collected data is combined and analysed using statistical methods to achieve a summary of findings.

The hierarchical evidence based medicine pyramid below (Figure 3) is a simple diagram made to illustrate the increasing strength of evidence and the lower risk of bias the further up the pyramid the study is situated.

Figure 3 Evidence Based Medicine Pyramide*



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* Filtered information means that a predefined search strategy has been employed to filter information and data used in the following synthesis and meta-analysis and unfiltered information means that the information derives directly from the studies described in the pyramide.

The Cochrane collaboration is an international network trying to produce evidence-based medicine of the highest quality, named after Archibald Leman Cochrane (1909-1988) who was an advocate for using the results of randomised controlled trials to make medicine more safe and efficient.[126] Cochrane collaborates with the World Health Organization (WHO) and 90% of WHO guidelines include Cochrane reviews among their references.[127] Systematic reviews are designed with the specific goal to minimise bias and are produced according to detailed eligibility criteria which are designed to answer specific research questions described in a pre-published protocol.[127] This is done by adhering to pre-specified systematic methods and procedures.[125]

The findings from Cochrane reviews are collated using GRADE (Grading of Recommendations, Assessment, Development and Evaluations), a framework for presenting summaries of evidence and grading the quality of evidence.[128]

1.9 Rationale for the thesis

The knowledge gaps which have motivated the work presented in the four papers in this thesis are summarised in the Table 1.

Table 1 Knowledge Gaps and Research Questions

Study	Knowledge gaps	Research Questions
I	Data on long-term follow-up after acute intravenous thrombolytic treatment are sparse.	Does thrombolytic treatment with alteplase improve long-term survival in patients with stroke?
II	Endovascular interventions are in rapid development and gaining significance in treatment of acute ischaemic stroke. Updated systematic reviews are warranted as several new randomised controlled trials have been published in recent years.	Are endovascular thrombectomy and/or other intra-arterial interventions plus medical treatment superior to medical treatment alone in patients with acute ischaemic stroke?
III	Wake-up stroke patients have traditionally been considered ineligible for acute treatment modalities as time of onset is unknown. Updated systematic reviews are warranted as several new randomised controlled trials have been published in recent years.	What is the efficacy and safety of intravenous thrombolytic treatment and endovascular thrombectomy versus control in patients with acute ischaemic stroke presenting on awakening?
IV	Randomised controlled trials have shown that highly selected wake-up stroke patients benefit from thrombolytic treatment with alteplase, but it is not known whether a wider range of wake-up stroke patients benefit from intravenous thrombolytic treatment. Tenecteplase has become the gold standard in the treatment of myocardial infarction and has showed promising results in randomised controlled trials for acute ischaemic stroke.	Can thrombolytic treatment with tenecteplase within 4.5 hours from time point of awakening with newly acquired stroke symptoms improve functional outcome at 90 days? Can findings on NCCT identify patients who benefit from thrombolytic treatment with tenecteplase?

2. AIMS OF THE THESIS

I. To assess the effect of intravenous alteplase on long-term survival after ischaemic stroke of participants in a large multicentre randomised controlled trial.

II. To assess the safety and efficacy of endovascular thrombectomy and intra-arterial interventions in patients with acute ischaemic stroke based on a meta-analysis of randomised controlled trials.

III. To assess the effects and safety of intravenous thrombolytic treatment and endovascular thrombectomy for acute ischaemic stroke presenting on awakening based on a meta-analysis of randomised controlled trials.

IV. To describe the rationale and design of a randomised controlled trial of thrombolytic treatment with tenecteplase in patients with acute ischaemic wake-up stroke.

3. MATERIAL AND METHODS

This thesis presents aspects on the effect of recanalisation therapies for acute ischaemic stroke in general and in wake-up stroke patients. It includes four papers; one randomised controlled trial, two systematic reviews with meta-analyses of randomised controlled trials, and the protocol of an ongoing randomised controlled trial.

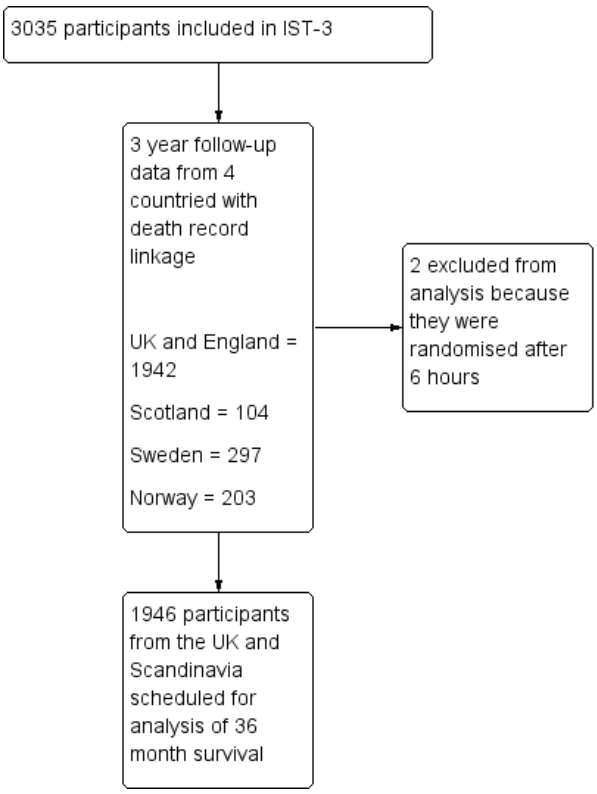
3.1 Paper I: IST-3

IST-3 was a prospective, open-label, randomised controlled trial with blinded endpoint design of thrombolytic treatment with alteplase in acute ischaemic stroke. IST-3 aimed to assess the balance of risk and benefit of thrombolysis more precisely and had a pragmatic design with broad entry criteria. The original target sample size was 6000 patients. The sample size was revised in 2007 because major changes in research regulations made it challenging to recruit patients.[129]

Patients with a definite acute ischaemic stroke who could be treated within 6 hours of stroke onset, with no upper age limit, were eligible for inclusion. Between May 2000 and July 2011, 3035 patients were enrolled from 156 participating centres in 12 countries. Patients were allocated in a 1:1 ratio using either a web-based or telephone randomisation system to intravenous alteplase (0.9 mg/kg) or to standard treatment alone. Participants from the United Kingdom, Sweden and Norway were selected for follow-up of survival up to 3 years due to the possibility for linkage to high quality national death registries in these countries. Figure 4 shows a participant flow diagram for the long-term 3 year follow-up analysis in IST-3.

IST-3 was carried out in accordance with the MRC Guidelines for Good Clinical Practice in Clinical Trials (United Kingdom) and in accordance with the EU directive on Clinical Trials.[130] The guidelines are based on the ICH Harmonised Tripartite Guideline for Good Clinical Practice and the Declaration of Helsinki. Local Ethics Committee approval was obtained for all participating centres before recruitment begun. All participants were enrolled after informed written consent was obtained. Consent forms were signed by either the participant or participant's legal representative when unable to sign themselves. The informed consent procedure was developed in line with recommendations and with consumer involvement. The information leaflet was adjusted to accommodate local ethical requirements.

Figure 4 IST-3 Participants Flow Diagram for 3-year survival analysis



Case fatality up to 3 years was compared in the intervention and standard treatment groups using Kaplan-Meier survival estimates. Analyses assessed whether the effect of alteplase was modified by age (≤80 years vs >80 years), stroke severity (NIHSS score ≤10 vs >10), or time to randomisation (≤3 h vs >3 h to ≤6 h). The likelihood ratio test was used to investigate whether multiplicative interaction terms improved the fit of a logistic regression model with survival status at 3 years as the dependent variable. Cox proportional hazards regression analysis comparisons were conducted on survival of the two groups. Whether the proportional effect of alteplase was constant over time was examined both by visual inspection and in a Cox regression model with inclusion of the main effect of treatment with a formal test of a multiplicative interaction term between treatment and time (≤7 days or >7 days). Because the hazards were non-proportional over time, separate calculations were performed of hazard ratios (HRs) in the early (≤7 days) and later (>7 days) periods. For survival after one week, follow-up was censored at 1096 days after randomisation and adjusted for the linear effects of the following: age, stroke severity (NIHSS score), and time to randomisation. A post-hoc analysis was done to further investigate the reason for the differences in long-term survival after one week that were not present in the overall case fatality analysis.

3.2 Paper II: Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke

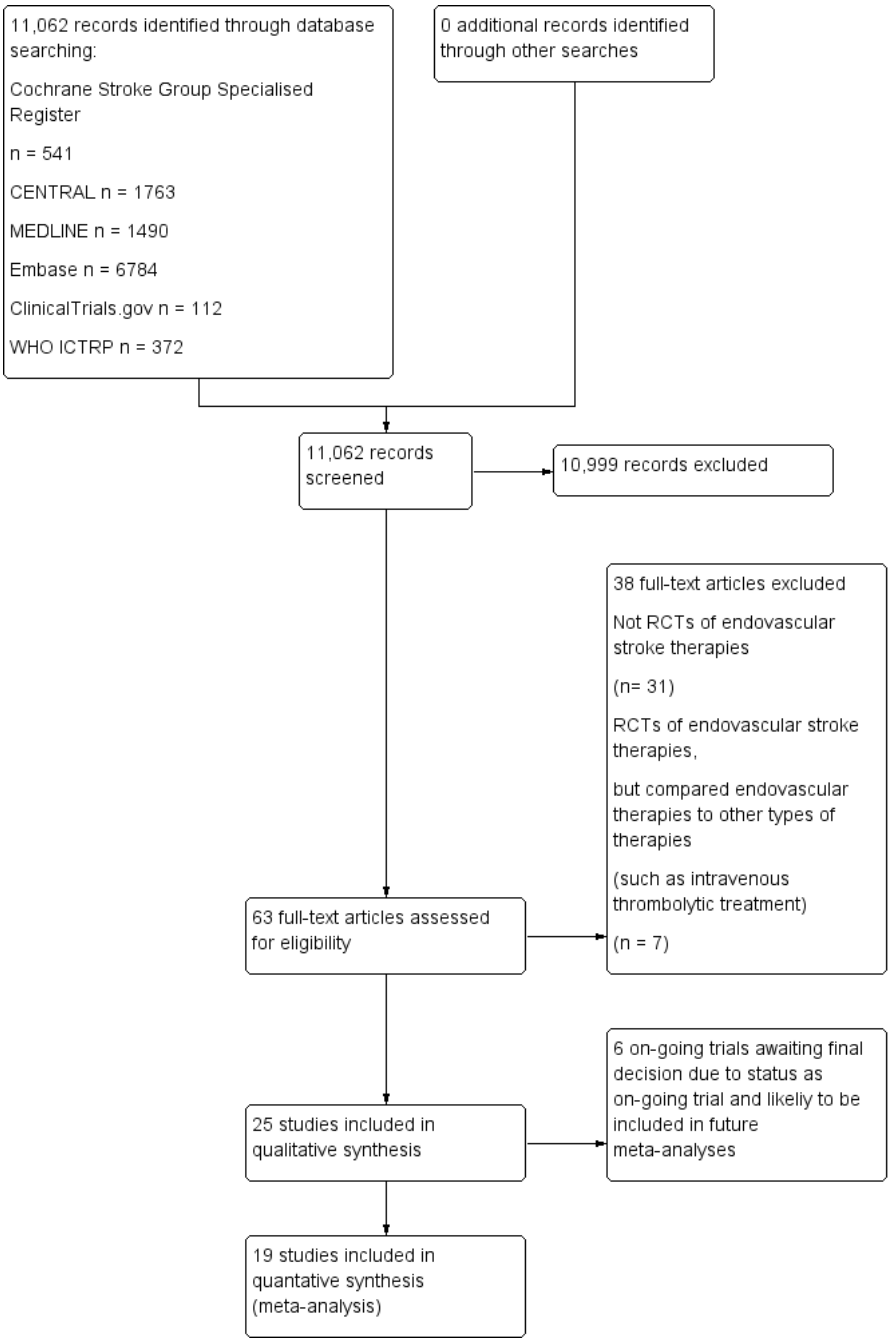
This meta-analysis aimed to include all randomised controlled trials of endovascular interventions of acute ischaemic stroke, both administration of thrombolytic drugs through intra-arterial catheters and/or the use of mechanical thrombectomy. Searches were performed in September 2020 in the following registers: the Cochrane Stroke Group Register, the Cochrane Database of Systematic Reviews Issue 9 of 12, September 2020, Ovid MEDLINE, US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov, WHO, International Clinical Trials Registry Platform (ICTRP), Cochrane Peripheral Vascular Diseases Group, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE. Trial registers were also searched. The searches were developed with the support of Cochrane's information specialist. We also screened the reference lists of articles identified by the search.

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for identification, selection and analysis of relevant studies.[131] Figure 5 show the PRISMA study flow diagram over all records found from all the searches and presents an overview of the selection process up until the 19 studies that were included in the meta-analysis.

Two of the authors independently screened titles and abstracts of references identified by the searches and assessed the full paper copy versions of the reports from these studies for inclusion. Any disagreements between the authors were resolved by discussion, and with the involvement from a third author if this proved to be necessary.

Only trials with participants with definite acute ischaemic stroke were included. All kinds of endovascular intervention techniques aimed at recanalisation in acute ischaemic stroke patients were eligible for inclusion: stent retrieval devices, angioplasty, mechanical fragmentation of the thrombus, thrombo-aspiration and intra-arterial thrombolysis. The comparison therapy was standard medical treatment, including intravenous thrombolytic treatment.

Figure 5 PRISMA Study Flow Diagram



The primary outcome was functional outcome at the end of scheduled follow up, defined by the mRS. mRS 0-2 was defined as good functional outcome and mRS 3-5 was defined as dependency. Secondary outcome measures included death from all causes during the first two weeks and at the end of scheduled follow up, and symptomatic intracerebral haemorrhage within the first 7 to 10 days. Symptomatic intracerebral haemorrhage was assessed according to both NINDS[54] and ECASS[55] criteria. Subgroup analyses of the primary endpoint were made for age, sex, stroke severity, mean time to groin puncture or initiation of treatment, intravenous

thrombolytic treatment, types of endovascular treatment, localisation of cerebral artery occlusion, location of occlusion and if penumbra imaging was used to select patients to treatment.

Measurement of treatment effects were for dichotomous outcomes a weighted estimate of treatment effects across the included trials. Risk ratios (RRs) were reported with 95% confidence intervals (CI). When continuous scales of measurement were used to assess the effects of treatment, there was an intention to use the mean difference. For studies that used different scales for assessment of similar outcomes, the intention was to report standardised mean differences.

The following strategy was employed to deal with missing data; In the sensitivity analysis it was 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.

Statistical and clinical heterogeneity was identified and measured as recommended in the Cochrane Handbook for Systematic Reviews of Interventions[125]. Heterogeneity between the included trials results were estimated using the I^2 statistic. The following thresholds were set for interpreting heterogeneity in the included trials: 0% to 30% no heterogeneity, 30% to 50% moderate heterogeneity, 50% to 80% substantial heterogeneity and 80% to 100% considerable heterogeneity. Evaluation of heterogeneity was not based on I^2 alone, since several factors are important. The assessment of heterogeneity was done after a thorough overall assessment of the available data.

We analysed the data using Review Manager 5 software (Review Manager 2020) and used binary logistic regression, the Mantel-Haenszel method.

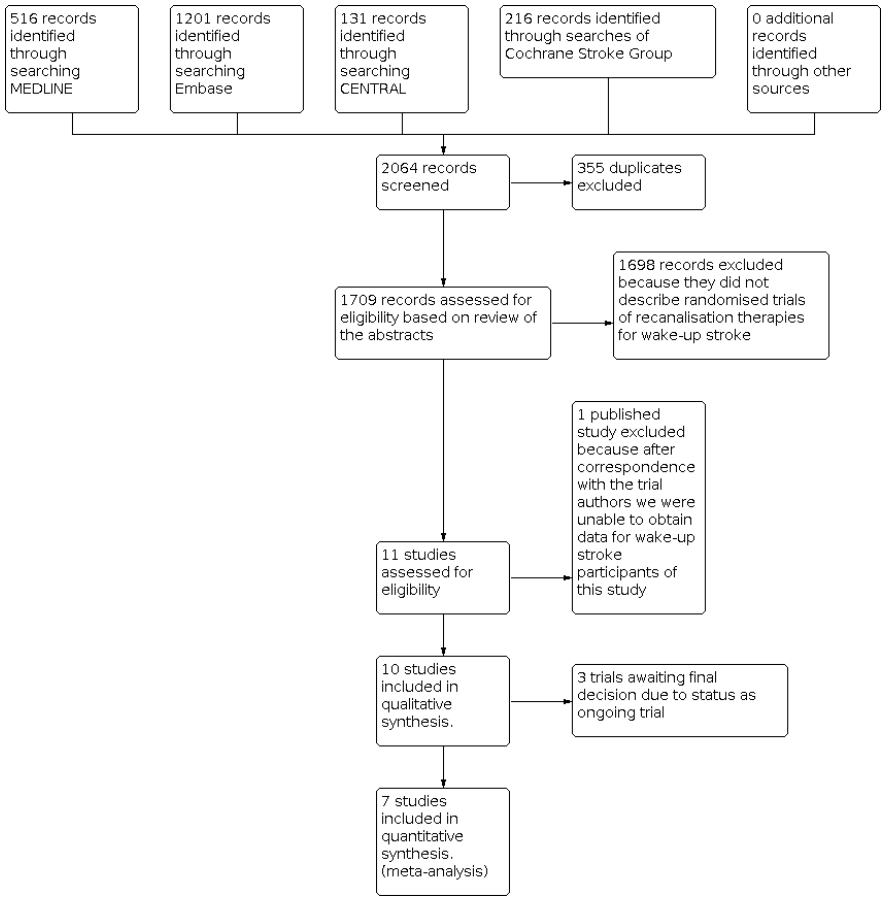
Risk ratios were derived and 95% confidence intervals for each included study. The results of the included studies were combined for each outcome. A random-effects model was used for pooled data and it was considered whether or not it was correct to pool data if considerable heterogeneity (I^2 value of 80% or more) was present across studies. Subgroup analyses were done using the methodology recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[125]

3.3 Paper III: Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic wake-up stroke

All randomised, controlled trials of recanalisations therapies, both intravenous thrombolytic therapies and endovascular mechanical thrombectomy, in patients with an acute ischaemic wake-up stroke, were eligible for inclusion in this review. A wake-up stroke was defined as a newly acquired stroke not present before sleep and where the patient is presenting new stroke symptoms upon awakening.

Searches were performed in May 2021 in the following electronic registers and databases: The Cochrane Stroke Group Trials Register, Cochrane Central Register of Controlled Trials Issue 4 of 12, MEDLINE Ovid, Embase, US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov., and WHO International Clinical Trials Registry Platform (ICTRP). We also screened references lists of relevant trials, contacted trialists and undertook forward tracking of relevant references. Figure 6 show the PRISMA study flow diagram over all records found from all the searches and presents an overview of the selection process up until the 7 studies that were included in the meta-analysis.

Figure 6 PRISMA Study Flow Diagram



Seven trials with 980 participants were included in this systematic review, 5 trials with 775 patients that tested intravenous thrombolytic treatment and 2 trials with 205 patients that tested endovascular thrombectomy in large vessel occlusion in the anterior segment. All trials used advanced imaging for selecting patients to treatment. When a randomised controlled trial had included both patients with a wake-up stroke and unknown onset stroke, we contacted the chief investigators and asked to receive data on patients with a wake-up stroke whilst excluding unknown onset stroke or other types of stroke. We received unpublished data for all the included trials of intravenous thrombolytic treatment for wake-up stroke.

The primary outcome was functional outcome defined as mRS 0-2 at end of follow-up which in all the included trials was 90 days. Secondary outcomes were death from all causes at the end of follow-up and symptomatic intracerebral haemorrhage at the end of follow-up. Subgroup analyses of the primary endpoint were made for age (< 60 years and > 60 years), sex, NIHSS (cutoff 10), large vessel occlusion diagnosed or not diagnosed on imaging and time from first observation of symptoms to onset of treatment (< 3 hours and > 3 hours).

The same statistical methods used in Paper II were used in Paper III.

3.4 Paper IV: TWIST

The purpose of the paper was to describe the rationale and design for an ongoing international multi-centre trial of thrombolytic treatment with tenecteplase versus standard care for acute ischaemic stroke, the Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST).

TWIST is designed as a prospective, open-label randomised controlled trial with blinded end-point assessment. We aim to include 600 patients (300 in each treatment arm) who can be treated within 4.5 hours upon awakening, and where non-contrast CT has excluded intracerebral haemorrhage and large infarction, defined as infarct size larger than 1/3 of the middle cerebral artery territory. Eligible for inclusion are patients aged 18 years or older with a clinical diagnosis of wake-up stroke with limb weakness and a NIHSS≥ 3, or dysphasia, who can be treated within 4.5 hours from time of awakening. Patients are randomly assigned to either intravenous tenecteplase or control with a 1:1 allocation using a central computer-generated randomisation schedule. The schedule employs a minimisation algorithm that balances age (<80 vs. ≥80 years), NIHSS severity (<15 and ≥15 points) and time from wake-up to randomisation (<3 hours and ≥ 3 hours).

The intervention dose of tenecteplase is 0.25 mg per kg of body weight (maximum 25 mg), given as an intravenous bolus. Both treatment arms receive best standard care, including intra-

arterial interventions for proximal cerebral artery occlusion when indicated according to the treating physician's best judgment.

The primary outcome is ordinal shift on the modified Rankin Scale at 3 months follow-up, assessed by a blinded for treatment interviewer and executed by a centralised telephone interview. Secondary effect variables include mRS 0-1 and 0-2 at 3 months, any intracerebral haemorrhage, symptomatic intracerebral haemorrhage, stroke progression during follow-up, recurrent ischaemic stroke during follow-up, major extracranial bleeding, and death from all cause during follow-up, NIHSS score at 24 hours and day 7, change in NIHSS score from baseline to 24 hours and day 7, Barthel Index score at 3 months, EuroCol score at 3 months and Mini Mental State Examination score at 3 months, as well as imaging and health economic variables.

Recruitment of patients started in July 2017 and ends on September 30, 2021. The following ten countries are participating: Norway, Sweden, Denmark, Finland, Lithuania, Estonia, Latvia, Switzerland, New Zealand and the United Kingdom.

Data will be analysed according to the intention-to-treat principle. Functional outcome assessed as shift across the full mRS scale at 3 months will be compared between the study groups by means of ordinal logistic regression, adjusted for age, baseline stroke severity (NIHSS) and time since wake-up. In secondary analyses, functional outcome will be dichotomised (mRS score 0-1 versus 2-6, and mRS 0-2 versus 3-6) and analysed by means of logistic regression, adjusting for age and symptom severity (baseline NIHSS score). All analyses will use a 5% two-sided level of significance.

The effect of treatment on survival will be assessed using Cox proportional hazards models adjusted for age and baseline NIHSS score and corresponding hazard ratios with 95% confidence intervals will be presented.

A detailed statistical analysis plan will be published prior to the locking of the database and analyses of data.

TWIST is carried out in accordance with the MRC Guidelines for Good Clinical Practice in Clinical Trials, the Council of Europe's Convention on Human rights and Biomedicine (CETS No.: 164), the ICH Harmonized Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) and the Declaration of Helsinki (Edinburgh, October 2000). Informed written consent is obtained from all participants or legal representative, according to legal requirements and ethical standards in each participating country. TWIST has received approval from medical research ethical committees and medical agencies in all participating countries prior to patient inclusion. In Sweden TWIST also received approval from the radiation

protection agency, as this is mandatory in this country. The trial was registered in ClinicalTrials.gov and the ISRCTN registry before the first patient was recruited into the trial.

A Patient Advisory Board with representatives from two Norwegian national organisations for stroke patients was established in the planning phase and is involved in all stages of the trial.

4. MAIN RESULTS

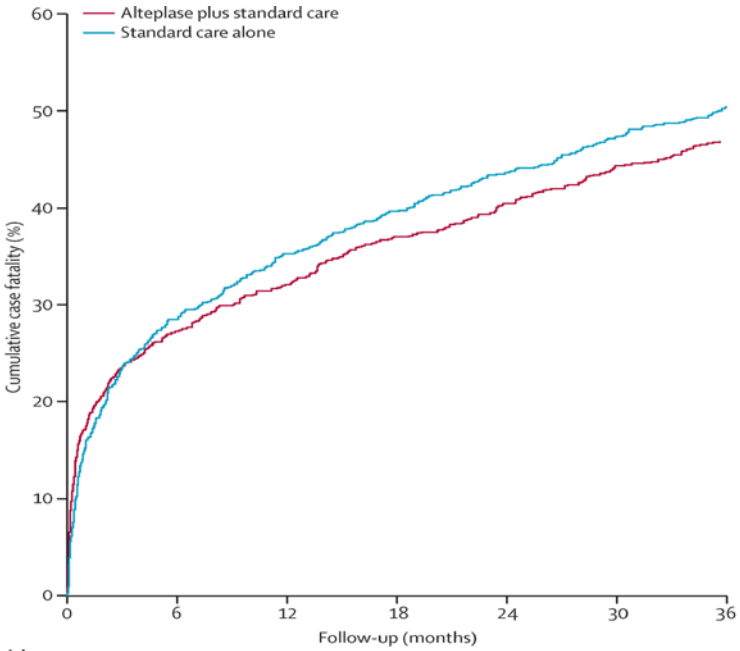
4.1 Paper I: IST-3

Information on long-term survival up to 3 years was available for 1948 of the originally 3035 IST-3 participants. Two patients were excluded because they had been randomised after 6 hours from stroke onset.

After 3 years of follow-up, 947 (49%) patients had died; 453 of 967 patients (46.8%) in the alteplase group and 494 of 979 (50.5%) in the control group.

At 36 months follow-up, there was a non-significant reduction in the proportion of participants that had died in the alteplase group plus standard care compared to standard care alone (risk difference 3,6%, 95% CI -0.8 to 8.1%, Figure 7).

Figure 7 Kaplan Meier curve - 3 years cumulative case fatality



Number at risk							
Alteplase plus standard care	967	703	657	609	576	538	514
Standard care alone	979	698	634	591	552	515	485
Cumulative number of deaths (%)							
Alteplase plus standard care	0	264 (27%)	310 (32%)	358 (37%)	391 (40%)	429 (44%)	453 (47%)
Standard care alone	0	281 (29%)	345 (35%)	388 (40%)	427 (44%)	464 (47%)	494 (51%)
Absolute risk difference (% [95% CI])	0	1·4% (−2·6 to 5·4)	3·2% (−1·0 to 7·4)	2·6% (−1·7 to 6·9)	3·2% (−1·2 to 7·6)	3·0% (−1·4 to 7·5)	3·6% (−0·8 to 8·1)

Because hazards were non-proportional during the study period, hazard ratios were calculated separately for the early (≤ 7 days) and late time period (> 7 days). In the early time period, participants allocated to alteplase plus standard care had a significantly higher hazard of death

compared to standard care alone (HR 1.52, 95% CI 1.11 to 2.08). In the late time period, participants allocated to alteplase plus standard care had a significantly lower hazard of death compared to standard care alone (HR 0.78, 95% CI 0.68 to 0.90). The results did not differ significantly for those aged ≤ 80 versus > 80 years, NIHSS score ≤ 10 versus > 10, or if they were treated ≤ 3 versus > 3 hours.

4.2 Paper II: Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke

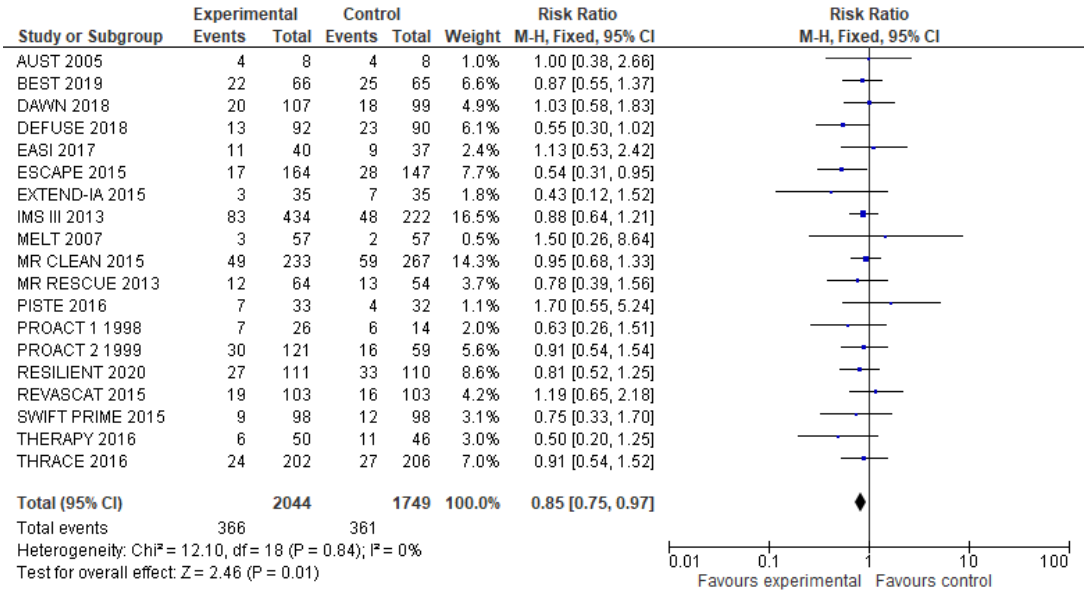
We included 19 studies with a total of 3793 participants (Table 2). The majority of participants had large artery occlusion in the anterior circulation and were treated within 6 hours of symptom onset. Data for analysis of the primary outcome, mRS 0-2, was available in 3715 patients from 18 trials.

Table 2 Overview of included studies in paper II

Type of intervention	N	Time from onset to treatment or imaging	Anterior circulation stroke	Posterior circulation stroke
IA thrombolysis only				
AUST	16	< 24 h	-	+
MELT	114	< 6 h	+ (MCA)	-
PROACT I	40	< 6 h	+ (MCA)	-
PROACT II	180	< 6 h	+ (MCA)	-
Thrombectomy				
THERAPY	96	No time limit/clot length of >8mm	+ (MCA)	
MR RESCUE	118	< 8 h	+	-
BEST	131	< 8 h	-	+
DAWN	206	6-24 h	+	-
DEFUSE 3	182	6-16 h	+	-
EASI	77	< 5 h or clinical/imaging mismatch	+	+
EXTEND IA	70	< 4.5 h	+ (MCA)	-
PISTE	65	< 6 h	+	-
RESILIENT	221	< 8 h	+	-
SWIFT PRIME	196	< 6 h	+	-
Thrombectomy and IA thrombolysis combined				
ESCAPE	311	< 12 h	+	-
IMS III	656	< 3 h	+	+
MR CLEAN	500	< 6 h	+	-
REVASCAT	206	< 8 h	+	-
THRACE	408	< 5 h	+	+

Treatment with intra-arterial endovascular procedures (thrombectomy and/or intra-arterial thrombolysis) increased the chance of achieving a good functional outcome, defined as mRS score 0-2: risk ratio (RR) 1.50, (95% CI 1.37 to 1.63). For mRS 0-1, data were available for a total of 3632 patients from 18 trials and showed a high effect in favour of treatment (RR 1.61, 95% CI 1.42 to 1.82). Treatment also reduced the risk of death at end of follow-up (RR 0.85, 95% CI 0.75 to 0.97, Figure 8) without increasing the risk of symptomatic intracranial haemorrhage in the acute phase (RR 1.46, 95% CI 0.91 to 2.36).

Figure 8 Death from all causes at the end of follow-up



4.3 Paper III: Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic wake-up stroke

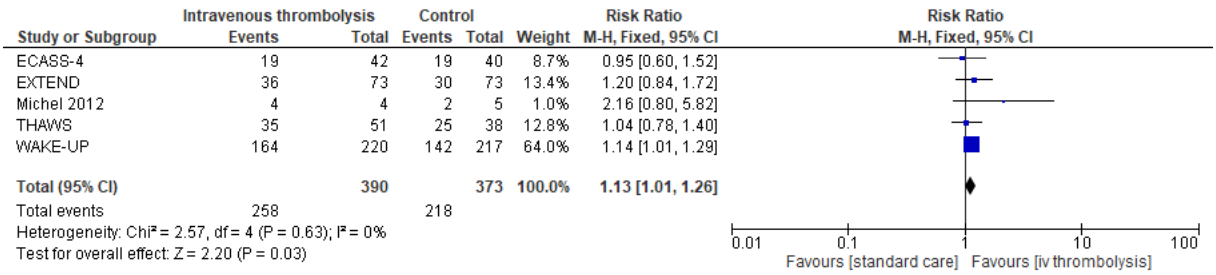
We identified 7 eligible studies with 980 wake-up stroke participants (Table 3). Five trials with 775 patients investigated the effect of intravenous thrombolytic treatment and two trials with 205 patients assessed the effect of endovascular thrombectomy in large vessel occlusion in the anterior intracranial circulation.

Table 3 Overview of the included trials in paper III

	N (total)	Wake-up stroke patients	Time to treatment in wake-up stroke patients	Advanced imaging selection	Drug Treatment modality	Results
Thrombolysis						
WAKE-UP	503	449	>4.5 h from last known well	MRI DWI/FLAIR mismatch	Alteplase 0.9 mg/kg	Positive
THAWS	131	89	>4.5 h last known well	MRI DWI/FLAIR mismatch	Alteplase 0.6 mg/kg	Neutral
EXTEND	225	146	>4.5-9 h or 9 h from midpoint sleep	Core/Penumbra mismatch on MRI or CTP	Alteplase 0.9 mg/kg	Positive
ECASS-4	119	82	>4.5-9 h from last known well	Core/Penumbra mismatch on MRI or CTP	Alteplase 0.9 mg/kg	Neutral
Michel et al	12	9	Treatment possible within 2 hours of hospital arrival	CTP	Alteplase 0,9 mg/kg	-
Thrombectomy						
DAWN	206	114	>6-24 hours	Clinical deficit/infarct volume mismatch	Mechanical thrombectomy	Positive
DEFUSE 3	182	91	>6-16 hours	Core/Penumbra mismatch	Mechanical thrombectomy	Positive

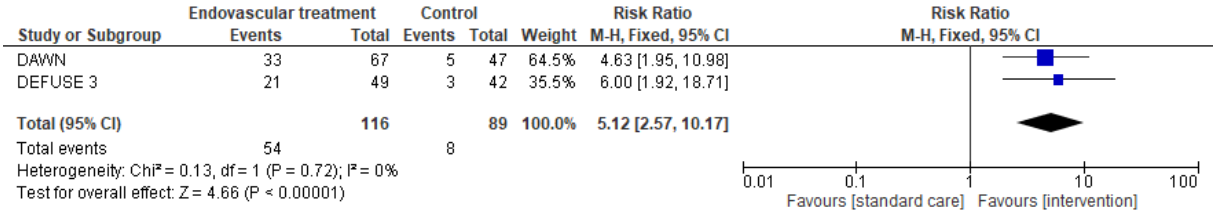
For intravenous thrombolytic treatment for acute ischaemic stroke, good functional outcome defined as modified Rankin Scale score 0-2 at 90 days follow-up was observed in 66% of participants randomised to thrombolytic treatment and 58% of participants randomised to control (RR 1.13, 95% CI 1.01 to 1.26, Figure 9). Seven percent 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). 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).

Figure 9 Good functional outcome at 90 days follow-up, defined as modified Rankin Scale score 0-2



Endovascular thrombectomy increased the chance of achieving good functional outcome (RR 5.12, 95% CI 2.57 to 10.17, Figure 10). Thrombectomy was also associated with a non-significant reduction in risk of death at end of follow-up (RR 0.68, 95% CI 0.43 to 1.07).

Figure 10 Good functional outcome at 90 days follow-up, defined as modified Rankin Scale score 0-2



Information on subgroup analysis on age, sex and NIHSS score was available in four of the randomised controlled trials of intravenous thrombolytic. There was no difference between the effects of the intervention in younger and older patients or between women and men. There was similar effect of thrombolytic treatment on functional outcome in participants with higher and participants with lower NIHSS score (RR 1.38, 95% CI 0.88 to 2.16) versus (RR 1.08, 95% CI 0.99 to 1.19).

4.4 Paper IV: TWIST

The trial started enrolment of patients in July 2017 and is still ongoing. Per September 18th 2021, 572 patients of planned target sample size of 600 patients have been included. Enrolment will end on September 30, 2021.

Open and closed annual reports have been sent to the Data Monitoring Committee, which has recommended that the trial should continue according to the protocol.

5. DISCUSSION

5.1 Paper I: IST-3

In this analysis of long-term survival in participants from the IST-3 trial scheduled for long-term follow-up, alteplase was associated with a non-significant 3.6% reduction in risk of death after 3 years. In the early time period (≤ 7 days), participants allocated to alteplase plus standard care had a significantly higher hazard of death compared to standard care alone. In the late time period (> 7 days), participants allocated to alteplase plus standard care had a significantly lower hazard of death compared to standard care alone.

The increased risk of death during the early time period may be attributed to intracerebral haemorrhages, a well-known complication of thrombolytic treatment.[54, 55] One plausible explanation of the reduced the risk of death in the late time period is that successful alteplase treatment result in reperfusion of penumbra and improve functional outcome. This is in line with results from previous studies that demonstrated that improved functional outcome is associated with improved long-term survival.[132, 133] An alternative explanation is that participants in the alteplase groups who died in the early period were older or had more severe strokes. If so, this would result in selection bias with participants in the alteplase group being younger and having less severe strokes in the late time period compared to participants in the control group. However, additional analysis adjusted for age and baseline stroke severity did not change the results and it is within reason to conclude that improved survival beyond the acute phase is an effect of treatment with alteplase.

The strength of this long-term survival analysis is that it was done with data from one of the larger randomised controlled acute stroke trials and that patients were followed-up over a longer time period than usual.

A weakness of the study is that long-term follow-up was not possible in all the originally included patients into the IST-3 trial. Despite a relatively large sample size, the statistical power is limited, especially when it comes to subgroup analyses. The subset of participants included in the long-term analysis were older, had more severe stroke and were randomised earlier than other patients in the IST-3 trial. There is a possibility that selection bias favours the alteplase group. The treatment of acute ischaemic stroke is advancing rapidly and the results from this analysis will not be applicable for patients receiving other treatment modalities or drugs.

IST-3 exemplifies some methodological challenges of conducting a randomised controlled trial.[134] First, recruitment of the pre-specified number of participants into the trial is often difficult if the treatment in question is already used in clinical practice.[135] When IST-3 was initiated, clinicians had used alteplase to treat acute ischaemic stroke for some years. Although further data was warranted, stroke clinicians may have been reluctant to randomise patients into

the trial as they believed alteplase was the best available treatment. The IST-3 trial co-ordinators encountered this problem and counteracted with giving informative talks and having an open discussion. Slow recruitment of patients can lead to trials taking far longer time to conclude than anticipated,[136] with risk of outdated trial design and research question upon completion. Most trials will experience difficulties not anticipated in the initial planning and early inclusion phases. This demands a high degree of flexibility of the trial management and an ability to adjust the trial conduct appropriately to be able to face the challenges that might arise.[137] In IST-3, the sample size was changed during the course of the trial because of changes in research regulations, making recruitment more challenging. Randomised controlled trials are generally highly resource demanding, time-consuming and they are also subject to trial fatigue.[138] If not carefully planned and executed, there is a risk that the study will become underpowered. This is highly problematic and ethically challenging as an underpowered study can ultimately turn out to be a waste of research resources.[139] It can also jeopardise patient trust and involvement both present and in the future. In addition, an underpowered trial can cause a premature discardment of new promising treatment modalities if it fails to show benefit. It is therefore a priority for the research community to find strategies to increase and simplify trial recruitment.[140] Isaksson et al identified the following important aspects: 1) the research question is perceived as important, 2) the consent and recruitment procedure is simple to perform, 3) motivated investigators and research nurses, and 4) follow-up procedure is pragmatic and feasible.[141] One suggestion to spare time, resources and simplify the follow-up procedure is to increasingly use digital or telecommunication alternatives to perform follow-up when possible.

5.2 Paper II: Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke

This systematic review and meta-analysis found high quality evidence for improved functional outcome associated with endovascular thrombectomy without increased risk of intracerebral haemorrhage or death.

The initial endovascular thrombectomy trials failed to show a positive effect of treatment on functional outcome.[88, 90] This changed in 2015 with the publication of the ground breaking MR CLEAN trial, rapidly followed by four other positive trials.[91-94, 142] This has been attributed to improved study design with more specified inclusion criteria, such as a defined time window for treatment within either 6[91, 92, 142] or 8 hours[94] and the use of improved equipment and stent-retrievers. Some of the later studies also excluded patients with poor collateral circulation and large infarction.[93, 94] Furthermore, the later trials also required certain criteria to be fulfilled for centres to qualify for participation in the trial, such as having performed a specified minimum amount of endovascular thrombectomy procedures, proven efficiency regarding rapid treatment times and/or documentation of a well-functioning work flow.[91, 93, 94]

It is important to note that the review includes both thrombectomy trials, trials of intra-arterial thrombolysis, or a combination of both. It also includes trials in the extended time window, as well as trials of thrombectomy in the posterior circulation. One of the reasons for this choice was that several of the included trials approved the use of both endovascular thrombectomy and intra-arterial interventions in the intervention arm of their participants.[88, 90, 93, 94, 143,91] This choice can be criticised for introducing unnecessary heterogeneity. To supply with complimentary data, we preformed several subgroup analyses. Assessment of heterogeneity was performed by using the I^2 statistic which describes the percentage of variation across studies that is due to heterogeneity rather than chance[125] and is reported for each subgroup analysis.

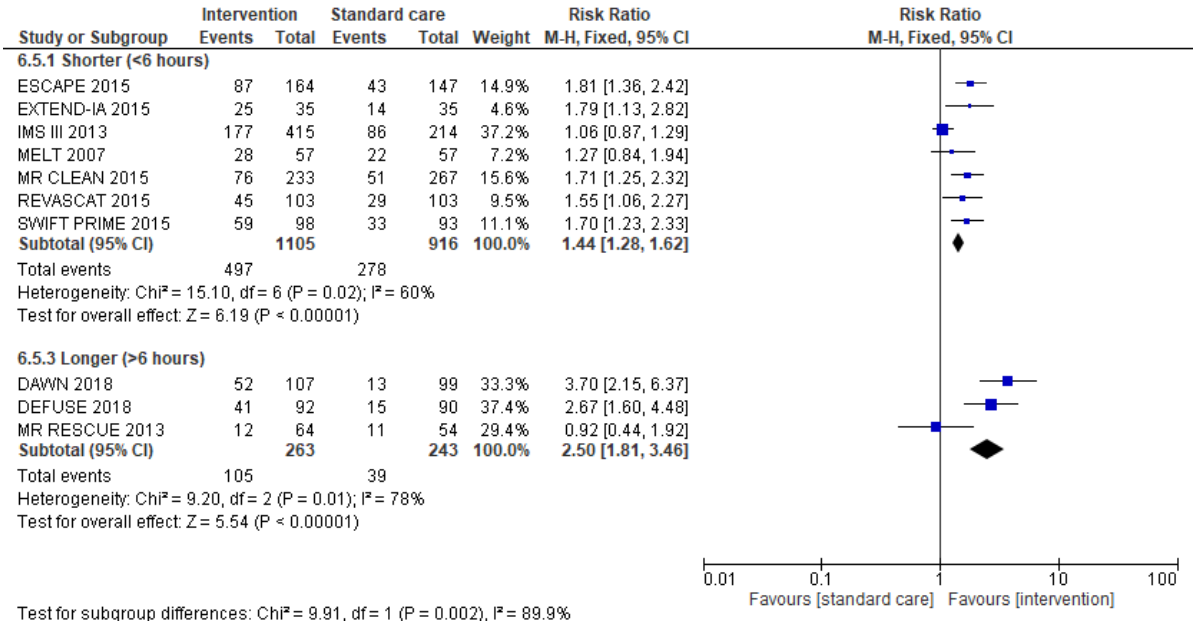
Analysis of trials of intra-arterial thrombolysis alone showed a positive effect on the main outcome, however the effect estimate was lower than in trials of thrombectomy and number of participants low. In another subgroup analysis, we compared the effect in participants treated with first generation mechanical devices and with stent-retrievers. As expected, the positive treatment effect was lower in trials using first-generation mechanical devices than in the later trials where a majority were treated with stent retrievers.

Whether so called "bridging treatment" with intravenous thrombolysis before endovascular treatment should be done or not has been subject of debate.[144] In our review, subgroup analysis on the use of intravenous thrombolytic treatment before randomisation showed similar benefit of endovascular thrombectomy regardless of whether bridging therapy was used or not.

While intervention on proximal arterial occlusions had a positive effect, we found no significant effect in trials which included both proximal and distal occlusions. Use of penumbra imaging or not for selection of patients did not show any difference on the effect of intervention.

In the published review, subgroup analyses were performed for mean time from stroke onset to groin puncture or initiation of intra-arterial treatment with available data from all included trials and divided these into intervals of <250 minutes, 250-300 minutes and >300 minutes. Studies in the extended time window up to 16 to 24 hours were excluded from this analysis. In an additional subgroup analysis (not included in paper II), we assessed the effect of thrombectomy and/or intra-arterial treatment in studies with mean time from onset to treatment within the 6 hours time window and studies of thrombectomy in the extended time window beyond 6 hours (Figure 11). The risk estimate for good functional outcome was higher in trials in the extended time window than in those in the first 6 hours interval. Heterogeneity was however high in both groups, probably due to clinical diversity. The shorter time window subgroup includes both thrombectomy and intra-arterial thrombolysis trials, as well as first and later generation equipment, while the longer time window subgroup includes thrombectomy trials where patients were selected by advanced imaging criteria.

Figure 11 Meta-analysis of mean time from stroke onset to groin puncture or initiation of intra-arterial treatment



Of note, a considerable number of the trials (16 of 19) included in the review were terminated prematurely and therefore suffer from a lack of statistical power. The strengths of this review are that it includes a rather high number of studies, that all trials reported their primary outcome by using the mRS and that all trials had scheduled their follow-up at the same time interval; 90 days. Extensive and thorough searches were performed and two review authors independently screened the literature for eligible studies. The review adhered to a pre-published protocol for data extraction and synthesis aimed to minimise bias.

5.3 Paper III: Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic wake-up stroke

This systematic review and meta-analysis showed a strong positive effect of thrombectomy on functional outcome after 90 days (RR 5.12, 95% CI 2.57 to 10) in selected patients with wake-up stroke and large vessel occlusion in the anterior circulation treated from 6 to 24 hours. In comparison, the corresponding risk ratio in DEFUSE 3 was 2.67 (95% CI 1.60 to 4.48) when all 192 patients (of whom 91 with wake-up stroke) were included.[96] In DAWN, the proportion with good functional outcome was 49% in the thrombectomy group and 13% in the control group when all 206 patients (114 with wake-up stroke) were included.[95] The reason for the larger effect seen in wake-up stroke patients is unknown, but one hypothesis is that the onset of stroke symptoms in patients with wake-up stroke is perhaps more likely to be in the lower spectrum of the 6-24 h window than in the higher. The circadian variation in ischaemic stroke

occurrence with a peak late in the morning can be interpreted in favour of this hypothesis,[102, 145, 146] as can the circadian variations of potential triggers such as blood pressure, paroxysmal atrial fibrillation and platelet aggregability.[105, 106]

In wake-up stroke the effect of intravenous thrombolytic treatment was moderate (RR 1.13, 95% CI 1.01 to 1.26). In the WAKE-UP trial, 53% of patients in the thrombolytic treatment group and 42% in the placebo group achieved a favourable outcome, being defined as modified Rankin Scale 0-1; this is a difference in the treatment effect which is comparable to that seen in patients receiving thrombolytic treatment within 3 hours after stroke symptom onset.[62] This effect was considerably weakened when the results from all trials were merged. Symptomatic intracranial haemorrhage occurred in 3% of participants in the treatment arm randomised to thrombolytic treatment and 1% in the control arm. The increased risk of symptomatic intracranial haemorrhage in patients that were randomised to thrombolytic treatment was of a marginal statistical significance (RR 3.47, 95% CI 0.98 to 12.26, p=0.05), and did not outweigh the positive effect of thrombolytic treatment on the primary functional outcome.

In several trials and reviews, good functional outcome has been defined as mRS 0-1,[62, 147] while others have defined good functional outcome as mRS 0-2.[55, 56, 95, 148] We chose to define mRS 0-2 as good functional outcome. This cutoff marks the transition zone between independence (mRS 0-2) and dependency in activities of daily life (mRS 3-5). There is no consensus on this matter, and other cutoffs could have given different results.

The strength of this review is that extensive and thorough searches were performed and that two review authors worked independently in screening for eligible studies and performing data extraction and synthesis. To minimise bias, the review adhered to a pre-published protocol. Another strength is that all included trials reported the primary outcome as the mRS after 90 days of follow-up. Another strength is that the meta-analysis includes previously unpublished data on the proportion of patients with a wake-up stroke from the included studies.

There are also some weaknesses. There were few trials eligible for inclusion: only 7 trials were included and the total number of participants was low. All included studies, except one, were terminated prematurely and consequently lack statistical power. The small-study effect is a term used to describe the phenomenon that smaller trials sometimes show different, often larger, treatment effects than the large trials.[149] Publication bias is one possible reason for the small-study effect. This can threaten the validity of systematic reviews and meta-analyses, as inclusion of smaller studies can result in inflated, more beneficial treatment effects.[125, 150] The lack of statistical power also has consequences for the subgroup analyses, which must be interpreted with caution.

5.4 Paper IV: TWIST

When TWIST was planned and initiated, no randomised controlled trials on thrombolytic treatment of wake-up stroke had been published, but four trials were ongoing. All ongoing trials used advanced imaging techniques such as MRI DWI/FLAIR mismatch criteria or MRI/CT penumbra imaging for selection of patients. Imaging aimed at detecting still viable brain tissue or strokes of short duration seems reasonable in the setting of wake-up stroke, as such techniques have the potential to identify the patients who are most likely to benefit from treatment as well as those with large, established infarction and higher risk of bleeding. On the other hand, there is a risk that selection of patients based on such techniques will exclude patients from receiving an effective treatment. Previous studies have shown that DWI/FLAIR mismatch can be absent in as many as 40% of patients with a stroke duration under 3 hours,[151] indicating that applying these criteria may exclude wake-up stroke patients who might benefit from thrombolysis from effective treatment. A previous randomised controlled trial which examined the value of advanced imaging for patient selection did not find a better effect of therapy in patients with penumbra, than in patients without penumbra.[152] Furthermore, advanced imaging techniques are more time-consuming and often not available in the emergency setting. Observational studies comparing patients with wake-up stroke and stroke with known onset within 4.5 hours did not show any difference in clinical or radiological findings.[99, 153-157] Thrombolytic treatment of wake-up stroke patients selected by non-contrast CT was found to be safe in a prospective, single-armed open-label safety trial from 2016.[158] Based on these observations, we felt that a randomised controlled trial using routinely available brain imaging criteria to select patients for treatment was warranted.

As described in a recent review and meta-analysis, neither of the advanced imaging techniques employed in published randomised controlled trials of wake-up stroke manage to encompass all patients that can benefit from treatment.[148] In the WAKE-UP trial, two thirds of patients screened for eligibility were not randomised, mainly because they did not have the required mismatch pattern on MRI DWI/FLAIR.[117] While MRI DWI FLAIR mismatch criteria will detect lacunar infarcts, these will not be detected by use of penumbral imaging with MR or CT perfusion as they will not meet the criteria for a relevant amount of salvageable tissue.[147] Observational studies have shown benefit of thrombolysis in wake-up stroke patients selected by non-contrast CT,[159] but this must be interpreted with caution as observational studies are prone to selection bias. As described above, TWIST aims to assess if patients who benefit from thrombolytic treatment can be identified by non-contrast CT.

Tenecteplase was chosen as the thrombolytic agent in TWIST for several reasons. It has several pharmacological advantages over alteplase[160] and has replaced alteplase for treatment of myocardial infarction.[73] Randomised controlled trials testing tenecteplase for acute ischaemic stroke with known onset within 4.5 hours have shown better recanalisation rates for

tenecteplase when given as bridging therapy before endovascular thrombectomy.[161] Tenecteplase have also been compared to alteplase in the treatment of acute ischaemic stroke within 4.5 hours in randomised controlled trials and have shown that it is as safe and effective as alteplase for acute ischaemic stroke.[74, 76, 80] This has led to change of recommendations in clinical guidelines.[38] Last, but not least, tenecteplase is easy and rapid to administrate as it only needs a single bolus dose and no infusion afterwards,[162] and this may be of importance in a situation where every minute counts.

As no available results from randomised controlled trials on thrombolytic treatment of wake-up stroke was available when TWIST was planned, we based the original sample size estimation on results from a meta-analysis of trials with patients with known time of stroke onset. This meta-analysis showed a 9% absolute difference in treatment effect between thrombolysed and non-thrombolysed patients, assessed as a binary endpoint (favourable outcome mRS 0-2 versus mRS 3-6).[148] Longer time from stroke onset to treatment in wake-up stroke patients compared to patients with known onset of stroke within 4.5 hours can be expected and this is likely to weaken the treatment effect. On the other hand, recent trials on patients with wake-up strokes actually have found similar and in some cases even larger differences between thrombolysed and non-thrombolysed patients with wake-up stroke and unknown stroke onset time.[117, 162] In the WAKE-UP trial, with a favourable outcome defined as mRS 0-1, the difference between thrombolysed and non-thrombolysed patients was 11.5%.[117] The same difference of 11.5% was also found in a meta-analysis of 6 observational studies on patients with unknown stroke onset time, where favourable outcome was defined as mRS 0-2.[163] The MRI based inclusion criteria in WAKE-UP compared to the CT-based inclusion in TWIST could lead to a smaller treatment effect in TWIST. Furthermore, selection bias in observational studies may result in larger treatment effect than in randomised controlled trials. However, it is possible that the effect size in TWIST will be closer to the observed effect in recent studies on wake-up stroke patients than to the effect in previous studies on patients with known time of symptom. The original sample size estimation in TWIST was therefore revised in 2020. A treatment effect of 10% absolute difference in a binary endpoint setting (mRS 0-1 versus mRS 2-6) was assumed and a distribution between mRS categories similar to that of the WAKE-UP trial with 42% with favourable outcome in the non-thrombolysed group vs 52% in the thrombolysed group, which corresponds to an odds ratio of 1.50. We assumed an mRS distribution in the control group similar to the control group in the WAKE-UP trial. The revised estimated sample size of 600 participants (with 300 participants per treatment arm) yields a power of 80%, a two-sided significance level of 5%, and an effect size specified as an odds ratio of 1.50 from an ordinal logistic regression model. Based on these estimations, the trial Steering Committee decided to increase the target sample size in TWIST from 500 to 600 patients.

Strengths of the trial is that it is a multi-centre, international randomised controlled trial. The randomisation procedure is performed centrally over the internet on a web-page requiring log-

in. To obtain balance between all participants a minimisation algorithm is employed for both age, stroke severity and time since wake-up. The 90 days follow-up assessment is performed by trained interviewers who are blinded to the given treatment.

There are some weaknesses. No placebo drug is used in this trial and because of the open design, neither patients nor investigators are blinded for treatment allocation. Even though the outcome assessment is done by blinded personnel, the open design as well as the nature of the main outcome, which is based on interviews of the patient (or carer), can be influenced by the patient's knowledge of the treatment allocation. This kind of bias can lead to enhancement of treatment effects. However, we assume that any such effect will be relatively small.

5.5 Implications for future research

Compared to trials of recanalisation therapies for acute myocardial infarction,[164, 165] the number of participants in similar stroke trials is small. More randomised controlled acute stroke trials are warranted to examine the effect of recanalisation therapies on wake-up stroke and for daytime onset unwitnessed stroke. Furthermore, more data are needed on the long-term effect on treatment in trial participants. To lower the costs, long-term outcome could be assessed by linkage to medical high-quality registries. It is also possible to consider alternative designs such as observational studies and register-based randomised controlled trials.

Endovascular thrombectomy for large vessel occlusion in the anterior circulation segment is safe and effective and recommended in guidelines.[38, 166] Existing guidelines does not recommend the use of endovascular thrombectomy of the posterior circulation because of lack of data from randomised controlled trials.[166] The only and recently published randomised controlled trial of treatment with endovascular thrombectomy in the posterior circulation was inconclusive and failed to prove benefit.[167] More and larger trials are warranted on this subject. It is also unclear whether medium sized and distal vessel occlusion should be treated with endovascular thrombectomy and more research regarding this matter is needed.[168] The optimal anesthesia management routine during endovascular thrombectomy remains uncertain. Existing guidelines does not recommend one technique over another.[38] A recently published review and meta-analysis of four randomised controlled trials comparing conscious sedation to general anesthesia found better recanalisation rates and functional outcome in patients who underwent general anesthesia during thrombectomy.[169] Analysis from a trial in the extended time window found higher likelihood for better functional outcome at 3 month follow-up in patients treated with thrombectomy under conscious sedation.[170] Larger randomised controlled trials are warranted.

When it comes to so called "bridging treatment" with intravenous thrombolysis before endovascular treatment results from a recent randomised controlled trial and meta-analysis

supported the use of bridging therapy prior to endovascular thrombectomy for large vessel occlusion.[171, 172] A currently ongoing randomised controlled trial aim at including 540 participants and will contribute with valuable data regarding this issue.[173]

When it comes to recommended brain imaging for acute ischaemic stroke non-contrast cerebral tomography (NCCT) has been proven to be a fast, readily available and effective way to detect and rule out acute intracerebral haemorrhage (ICH). This was the only brain imaging modality used in the initial stroke trials.[54, 59] Studies comparing magnetic resonance imaging (MRI) to NCCT for detection of ICH have led to changes in guidelines as they have shown similar accuracy.[38, 174, 175] In patients eligible for thrombectomy it is recommended to perform CT angiography to identify the site of occlusion and assess status of collaterals. In all randomised controlled trials of recanalisation therapies for patients with wake-up stroke and in the extended time window, advanced imaging such as cerebral tomography perfusion (CTP) or MRI penumbra imaging and MRI DWI/FLAIR mismatch criteria are used for selection of patients to treatment. None of these imaging techniques have been shown to be superior in selecting patients who benefit from treatment. No ongoing randomised controlled trials on this subject was identified when writing this thesis. However, randomised controlled trials designed to test the different imaging techniques in the acute setting may be difficult to design and perform as they would be time-consuming and therefore ethically challenging and may not be feasible to undertake.

Several randomised controlled trials for acute ischaemic stroke comparing intravenous thrombolytic treatment with alteplase versus tenecteplase are on-going.[78, 176] The results of these trials will add important data and hopefully clarify whether tenecteplase can be an approved and equal alternative or even superior to alteplase in treatment of acute ischaemic stroke.

6. CONCLUSIONS

I. Thrombolytic treatment with alteplase within 6 hours after onset of acute ischaemic stroke was associated with a non-significant reduction in risk of death after 3 years in a sub-set of participants in the randomised controlled trial IST-3. Among participants who survived the first week, thrombolytic treatment was associated with a significant improvement in survival after 3 years follow-up.

II. Endovascular thrombectomy is safe and effective in patients with acute ischaemic stroke due to large artery occlusion in the anterior circulation.

III. Endovascular thrombectomy treatment is safe and highly effective in acute ischaemic stroke with large vessel occlusion in the anterior segment in selected wake-up stroke patients up to 24 hours after symptom onset. Intravenous thrombolytic treatment was also associated with benefit in selected patients with wake-up stroke.

IV. The on-going randomised controlled trial TWIST aims to establish whether thrombolytic treatment with tenecteplase within 4.5 hours from awakening with a wake-up stroke reduces the risk of poor functional outcome at 90 days and if findings on non-contrast CT, can identify patients that benefit from thrombolytic treatment with tenecteplase.

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Paper I

Berge E, Cohen G, Roaldsen MB, Lundström E, Isaksson E, Rudberg A-S, Slot KB, Forbes J, Smith J, Drever J, Wardlaw JM, Lindley RI, Sandercock PAG, Whiteley WN

Effects of alteplase on survival after ischaemic stroke (IST-3): 3-year follow-up of a randomised, controlled, open-label trial

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Effects of alteplase on survival after ischaemic stroke (IST-3): 3 year follow-up of a randomised, controlled, open-label trial

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Summary

Background **The effect of alteplase on patient survival after ischaemic stroke is the subject of debate. We report the effect of intravenous alteplase on long-term survival after ischaemic stroke of participants in the Third International Stroke Trial (IST-3).**

Methods **In IST-3, done at 156 hospitals in 12 countries (Australia, Europe, and the UK), participants (aged >18 years) were randomly assigned with a telephone voice-activated or web-based system in a 1:1 ratio to treatment with intravenous 0·9 mg/kg alteplase plus standard care or standard care alone within 6 h of ischaemic stroke. We followed up participants in the UK and Scandinavia (Sweden and Norway) for survival up to 3 years after randomisation using data from national registries and compared survival in the two groups with proportional hazards survival analysis, adjusting for key prognostic variables. IST-3 is registered with the ISRCTN registry, number ISRCTN25765518.**

Findings **Between May 5, 2000, and July 27, 2011, 3035 participants were enrolled in IST-3. Of these, 1948 (64%) of 3035 participants were scheduled for analysis of 3 year survival, and 1946 (>99%) of these were included in the analysis (967 [50%] in the alteplase plus standard care group and 979 [50%] in the standard care alone group). By 3 years after randomisation, 453 (47%) of 967 participants in the alteplase plus standard care group and 494 (50%) of 979 in the standard care alone group had died (risk difference 3·6% [95% CI –0·8 to 8·1]). Participants allocated to alteplase had a significantly higher hazard of death during the first 7 days (99 [10%] of 967 died in the alteplase plus standard care group *vs* 65 [7%] of 979 in the standard care alone group; hazard ratio 1·52 [95% CI 1·11–2·08]; p=0·004) and a significantly lower hazard of death between 8 days and 3 years (354 [41%] of 868 *vs* 429 [47%] of 914; 0·78 [0·68–0·90]; p=0·007).**

Interpretation **Alteplase treatment within 6 h after ischaemic stroke was associated with a small, non-significant reduction in risk of death at 3 years, but among individuals who survived the acute phase, treatment was associated with a significant increase in long-term survival. These results are reassuring for clinicians who have expressed concerns about the effect of alteplase on survival.**

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Introduction

Timely treatment with alteplase for acute ischaemic stroke improves functional outcome by 3–6 months,[1,2] but has not been shown to improve survival, and questions have been raised about the long-term benefit of treatment.[3–5] Alteplase increases the risk of death during the first week of treatment, mainly because of intracranial haemorrhage, but this increase is later offset by a risk reduction so that, by 3–6 months, no excess of deaths occurs among patients treated with alteplase.[1,2] Investigators of the National Institute of Neurological Disorders and Stroke trial[6] and the Third International Stroke Trial (IST-3)[7] followed up participants beyond the first 3–6 months and found no significant effect of alteplase on case fatality at 12 months[8] or 18 months.[9,10] However, a difference might arise after longer follow up than 18 months if improvements in functional outcome translate into survival benefits over time, as suggested by findings from observational studies.[11,12] To examine this hypothesis and provide further evidence on the long-term effects of alteplase, we assessed survival up to 3 years among participants enrolled in IST-3 in the UK and Scandinavia (Sweden and Norway), where long-term follow-up was possible by linkage to routinely collected data in national death registries.

Methods

Study design and participants

IST-3[7] was a randomised, open-label trial of alteplase plus standard care versus standard care alone within 6 h of ischaemic stroke done at 156 hospitals in 12 countries (Australia, Austria, Belgium, Canada, Italy, Mexico, Norway, Poland, Portugal, Sweden,

Research in context

Evidence before this study

We searched the literature as part of an ongoing, periodically updated Cochrane Review on thrombolytic treatment for acute ischaemic stroke. We searched the Cochrane Stroke Group Trials Register, MEDLINE (since Jan 1, 1966), Embase (since Jan 1, 1980), stroke journals, conference proceedings, and ongoing clinical trials registers. We also contacted investigators and pharmaceutical companies. We searched using the terms "acute ischaemic stroke", "thrombolysis", "thrombolytic therapy", "alteplase", and "recombinant tissue plasminogen activator". We did not use language restrictions and included all randomised trials of alteplase versus control in patients with definite ischaemic stroke. Only the National Institute of Neurological Disorders and Stroke (NINDS) trial and the Third International Stroke Trial (IST-3) followed up participants for longer than 3–6 months. The NINDS trial included 624 participants who were followed up for 12 months, whereas IST-3 included 3035 participants and has previously reported follow-up for 18 months. Alteplase was not shown to improve survival, and questions have been raised about the long-term benefit of treatment.

Added value of this study

In this study, we report additional follow-up to 3 years of 1948 participants in IST-3 from the UK, Sweden, and Norway. The analysis of survival to 3 years showed a small, non-significant reduction in the risk of death by end of follow-up, but among those who survived the acute phase, we found a significant improvement in survival up to 3 years.

Implications of all the available evidence

These results are reassuring for clinicians who have been unsure about the benefits of alteplase and for patients who have an option to trade an early increased hazard with long-term benefits. The effect on survival adds to the long-term beneficial effects of alteplase on functional outcome and quality of life and reinforces the case for alteplase for ischaemic stroke.

Switzerland, and the UK). The main eligibility criteria were age higher than 18 years; symptoms and signs of clinically definite acute stroke; ability to start treatment within 6 h of stroke onset; and exclusion with CT or MRI of intracranial haemorrhage and structural brain lesions, which could mimic stroke (eg, cerebral tumour). The main exclusion criteria were major surgery, trauma, or gastrointestinal or urinary tract haemorrhage within the previous 21 days; arterial puncture at a non-compressible site within the previous 7 days; and any known defect in coagulation, clotting, or platelet function. Continued follow-up of participants for up to 3 years was planned in the UK, Sweden, and Norway because linkage to routinely collected death records was feasible. Participants or their proxies gave written informed consent. The protocol of the trial was approved by research ethics committees in all three countries. Details of the protocol[13,14] and the main results[7] have been published previously.

Randomisation and masking

In IST-3, investigators entered baseline data using a telephone voice-activated or web-based system that randomly assigned participants to open-label alteplase plus standard care or standard care alone in a 1:1 ratio. Randomisation was stratified by region from Jan 1, 2006 (Sweden and Norway were one region, and the UK constituted most of another region) and used a minimisation algorithm to balance treatment groups with respect to key prognostic variables (age, National Institutes of Health Stroke Scale [NIHSS] score, time to randomisation, use of antiplatelet agents, and stroke subtype).[15]

Procedures

Patients received intravenous alteplase at 0·9 mg/kg (10% as a bolus and 90% over the next hour) plus standard care or standard care alone within 6 h of ischaemic stroke. Follow-up in IST-3 was by clinical visit at 7 days (or at discharge, whichever occurred first) and by postal questionnaire or telephone interview at 6 months and 18 months.[7,9,10] In the UK and Scandinavian countries, participants were also followed up for survival until 3 years by checking the central death registries. For this analysis, we also included participants from the UK who were recruited after June 30, 2010, and therefore could not be included in a previous 18 month analysis of survival, functional outcome, and health-related quality of life up to Jan 30, 2012.[9] Since registration of deaths is complete in the UK and Scandinavia, we assumed that participants were still alive if they had no death record up to 1096 days, and we did not take account of emigration, which we assumed to be small (between <1% and 2% of the general population per year, and probably smaller in patients with stroke). For all deaths in the first 7 days, the cause of death was assigned by the event adjudication committee. For deaths after 7 days, a broad classification of cause of death was made centrally on the basis of the extent of information received from national registries or general practitioners.

Outcomes

The primary outcome in IST-3 was the proportion of patients alive and independent at 6 months, and the key secondary outcomes have been reported previously.[7,9,10] In this study, we report survival up to 3 years after randomisation.

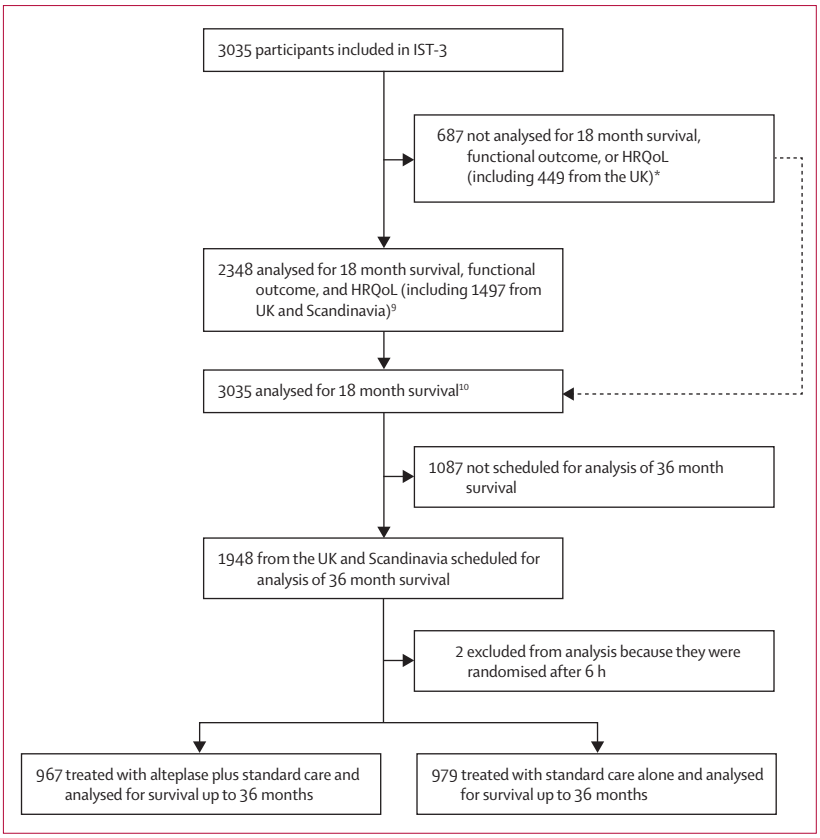


Figure 1: **Trial profile**

IST-3=Third International Stroke Trial. HRQoL=health-related quality of life. *Patients were recruited after June 30, 2010, and so could not be included in the dataset used in the 18 month analysis,[9] which was closed on Jan 30, 2012.

	Alteplase plus standard care (n=967)	Standard care alone (n=979)
Age (years)	82 (73–86)	82 (72–86)
Women	498 (51%)	501 (51%)
National Institutes of Health Stroke Scale score	11 (7–18)	11 (7–17)
Systolic blood pressure (mm Hg)	156 (139–174)	156 (140–173)
Atrial fibrillation	313 (32%)	300 (31%)
Time to randomisation (h)	3·8 (2·8–4·7)	3·7 (2·8–4·7)
Stroke syndrome*		
Total anterior circulation syndrome	446 (46%)	474 (48%)
Partial anterior circulation syndrome	364 (38%)	326 (33%)
Posterior circulation syndrome	56 (6%)	81 (8%)
Lacunar syndrome	100 (10%)	97 (10%)
Infarct size†‡		
No infarct visible	556 (57%)	594 (61%)
Small or medium	242 (25%)	222 (23%)
Large or very large	169 (17%)	162 (17%)

Data are median (IQR) or n (%). *Could not be classified for one case in each group. †Could not be classified for one case in the standard care alone group. ‡Measured by CT scan in 99% of cases (and MRI in the rest of the cases), as described in Wardlaw and Sellar.[16]

Table 1: **Baseline characteristics**

Statistical analysis

In this follow-up study, we compared case fatality up to 3 years in the alteplase plus standard care and standard care alone groups using Kaplan-Meier survival estimates, and assessed whether the effect of alteplase was modified by age (≤80 years *vs* >80 years), stroke severity (NIHSS score ≤10 *vs* >10), or time to randomisation (≤3 h *vs* >3 h to ≤6 h) by using a likelihood ratio test to investigate whether multiplicative interaction terms improved the fit of a logistic regression model with survival status at 3 years as the dependent variable. We based the thresholds for the definition of subgroups (age and NIHSS score) on the European licence for alteplase for acute stroke or previous work.[1]

We also compared survival of the two groups with Cox proportional hazards regression analysis. We examined whether the proportional effect of alteplase was constant over time, both graphically and with a formal test of a multiplicative interaction term between treatment and time (≤7 days or >7 days) in a Cox regression model, which also included the main effect of treatment. We anticipated that hazards would be non-proportional for the whole period, so we separately calculated hazard ratios (HRs) in the early (≤7 days) and later (>7 days) periods. For survival beyond 7 days, we censored follow-up at 1096 days after randomisation and adjusted for the linear effects of age, stroke severity (NIHSS score), and time to randomisation. We also examined whether the effect of treatment in these periods was modified by age (≤80 years *vs* >80 years), stroke severity (NIHSS score ≤10 *vs* >10), or time to randomisation (≤3 h *vs* >3 h to ≤6 h) by establishing whether interaction terms improved the fit of the Cox proportional hazards model.

In a post-hoc analysis, to understand the reason for differences in long-term survival after 7 days but not in overall case fatility from day 0, we compared age, stroke severity, and time to randomisation at baseline between participants who died during the first 7 days and those who survived the first 7 days, both in the alteplase plus standard care and standard care alone groups. We did analyses with SAS (version 9.4). IST-3 is registered with the ISRCTN registry, number ISRCTN25765518.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 5, 2000, and July 27, 2011, 3035 participants were enrolled in IST-3 (figure 1). 1515 (50%) were assigned to the alteplase plus standard care group and 1520 (50%) were assigned to the standard care alone group. Of the 3035 participants in the trial, 1948 (64%) participants were recruited in the UK and Scandinavia and were

scheduled for analysis of 3 year survival. Two (<1%) participants who were randomised after 6 h were excluded from this analysis and, of the remaining 1946 (>99%) participants (967 [50%] in the alteplase plus standard care group and 979 [50%] in the standard care alone group), 1446 (74%) were recruited in the UK, 297 (15%) were recruited in Sweden, and 203 (10%) were recruited in Norway. Participants from the UK included 449 who were recruited after June 30, 2010, and were therefore not eligible for a previous 18 month analysis (figure 1).[9] Baseline characteristics were well balanced between participants in the alteplase plus standard care and standard care alone groups (table 1).

At 7 days, 99 (10%) of 967 participants in the alteplase plus standard care group and 65 (7%) of 979 participants in the standard care alone group had died (risk difference 3·6% [95% CI 1·1–6·1]). During the 3 year follow-up, the proportions of participants who had died at 6 months, 18 months, and 36 months were non-significantly lower in the alteplase plus standard care group than in the standard care alone group (figure 2). At 3 years, 453 (47%) of 967 participants in the alteplase plus standard care group and 494 (50%) of 979 participants in the standard care alone group had died (risk difference 3·6% [95% CI –0·8 to 8·1]; figure 2; table 2). Subgroup analyses of differences in case fatality at 3 years suggested that age (≤80 years *vs* >80 years), stroke severity (NIHSS score ≤10 *vs* >10), or time to randomisation (≤3 h *vs* >3 h to ≤6 h) did not modify the effect of alteplase (table 2).

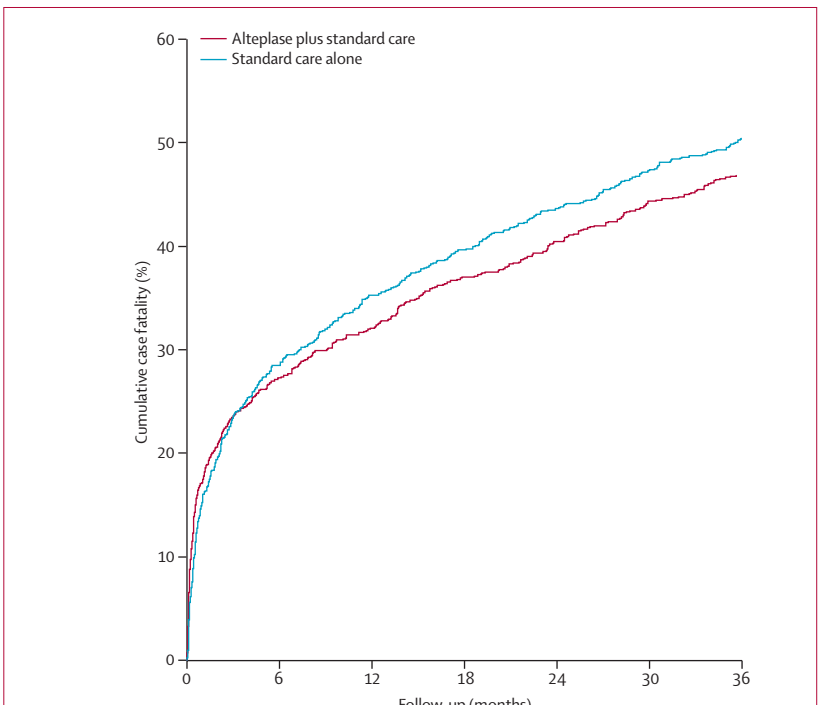
Hazards were non-proportional for the whole time period (p<0·0001; data not shown), so we separately calculated HRs in the early (≤7 days) and late (>7 days) time periods. Within the late time periods (8 days to 18 months and 18–36 months), we found no evidence that hazards were non-proportional (p=0·98; data not shown). Compared with the hazard of death in participants in the standard care alone group, the hazard of death with alteplase plus standard care was significantly higher during 0–7 days (99 [10%] of 967 participants in the alteplase plus standard care group *vs* 65 [7%] of 979 in the standard care alone group; HR 1·52 [95% CI 1·11–2·08]; p=0·004) and significantly lower from 8 days to 3 years (354 [41%] of 868 *vs* 429 [47%] of 914 participants; HR 0·78 [0·68–0·90]; p=0·007; figure 3). We found no effect modifications by age, stroke severity, or time to randomisation using the same (figure 3) or alternative subgroup classifications or modelling with continuous variables (data not shown).

The proportion of deaths up to 7 days due to intracranial haemorrhage or swelling of the original infarct was significantly greater in the alteplase plus standard care group than in the standard care alone group (appendix p 1; p<0·0001 for χ^2 test of difference in all-cause death). We found no significant difference in cause of death between the alteplase plus standard care and standard care alone groups after 7 days (appendix p 1; difference in all-cause death p=0·18).

We checked whether differences in survival after 7 days could be explained by imbalances in important prognostic variables between treatment groups at 7 days (appendix p 2). As expected, participants who died during the first 7 days had more severe stroke at baseline than did those who survived the first 7 days, but this finding was similar in the alteplase plus standard care and standard care alone groups, and we found no evidence of an imbalance in age, stroke severity, or time to randomisation between the treatment groups among survivors at 7 days.

Finally, since our analysis was done in a subset of all participants in IST-3, we compared the baseline characteristics of participants in our subset dataset with those of the other participants in IST-3, and found that participants in our analysis were older, had higher systolic blood pressure, had atrial fibrillation more often, had more severe strokes, and were randomised to treatment

See Online for appendix



Number at risk							
Alteplase plus standard care	967	703	657	609	576	538	514
Standard care alone	979	698	634	591	552	515	485
Cumulative number of deaths (%)							
Alteplase plus standard care	0	264 (27%)	310 (32%)	358 (37%)	391 (40%)	429 (44%)	453 (47%)
Standard care alone	0	281 (29%)	345 (35%)	388 (40%)	427 (44%)	464 (47%)	494 (51%)
Absolute risk difference (% [95% CI])	0	1·4% (–2·6 to 5·4)	3·2% (–1·0 to 7·4)	2·6% (–1·7 to 6·9)	3·2% (–1·2 to 7·6)	3·0% (–1·4 to 7·5)	3·6% (–0·8 to 8·1)

Figure 2: **3 year cumulative case fatality**

	Alteplase plus standard care (n=967)		Standard care alone (n=979)		Risk difference (%; 95% CI)	p value for interaction*
	Deaths (n)	Kaplan-Meier estimate (%; 95% CI)	Deaths (n)	Kaplan-Meier estimate (%; 95% CI)		
All patients (n=1946)	453	46·8% (43·7 to 50·0)	494	50·5% (47·3 to 53·6)	3·6% (−0·8 to 8·1)	..
Age (years)						0·57
≤80 (n=827)	119	29·3% (24·9 to 33·7)	133	31·6% (27·2 to 36·0)	2·3% (−4·0 to 8·6)	..
>80 (n=1119)	334	59·5% (55·5 to 63·6)	361	64·7% (60·7 to 68·7)	5·2% (−0·5 to 10·8)	..
National Institutes of Health Stroke Scale score						0·84
≤10 (n=894)	137	31·3% (26·9 to 35·6)	158	34·6% (30·3 to 39·0)	3·4% (−2·8 to 9·5)	..
>10 (n=1052)	316	59·7% (55·6 to 63·9)	336	64·2% (60·1 to 68·4)	4·5% (−1·4 to 10·4)	..
Time to randomisation (h)						0·89
≤3 (n=613)	168	54·7% (49·2 to 60·3)	180	58·8% (53·3 to 64·3)	4·1% (−3·7 to 11·9)	..
>3 to ≤6 (n=1333)	285	43·2% (39·4 to 47·0)	314	46·7% (42·9 to 50·4)	3·5% (−1·9 to 8·8)	..

*From logistic regression model with survival status at 3 years as a dependent variable.

Table 2: **Kaplan-Meier estimates of 3 year case fatality**

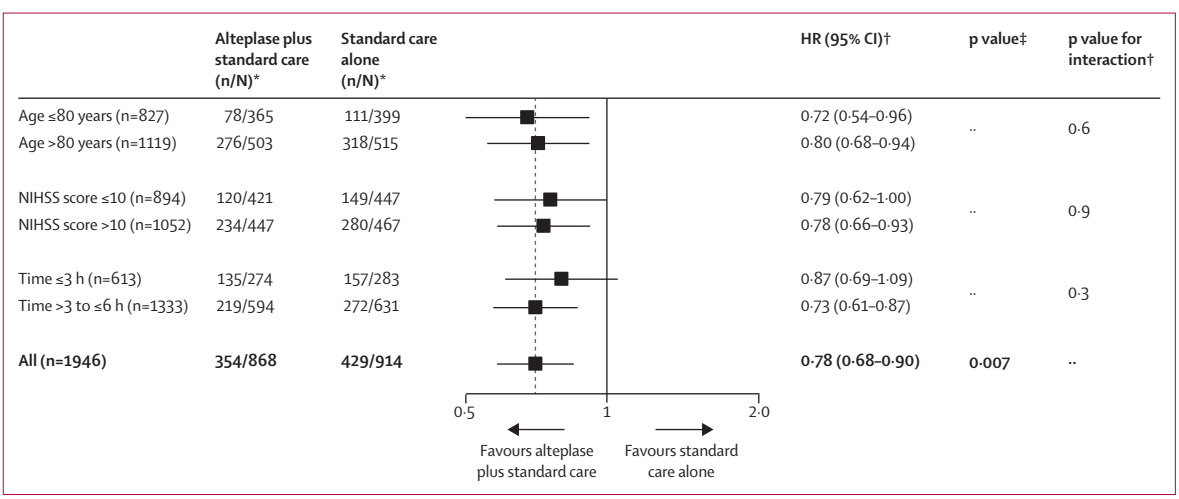


Figure 3: **Hazard ratios for death from 8 days to 3 years**

HR=hazard ratio. NIHSS=National Institutes of Health Stroke Scale. *Number of patients who died during 8 days to 3 years divided by number of patients alive at 8 days. †From Cox regression analysis, adjusted for age, NIHSS score, and time to randomisation. ‡From log-rank test of difference in survival.

earlier than the other 1087 participants in IST-3 (appendix p 3). We also analysed survival beyond 7 days in the datasets previously used for analysis of survival up to 18 months[9,10] and found HRs that were broadly similar to those of the dataset used in this study (appendix pp 4–5).

Discussion

In this analysis of the near two-thirds of participants in IST-3 scheduled for long-term follow-up, we found that alteplase was associated with an absolute reduction of 3·6% in the risk of death at 3 years, which was not significant. We also found that participants allocated alteplase plus standard care who survived to 7 days had a significantly better survival up to 3 years than did those allocated standard care alone. These findings mean that, even if alteplase increases the risk of intracranial haemorrhage and death in the acute phase, patients can be assured that, in the long term, risk of death is not increased with alteplase and that, if they survive to 1 week, alteplase increases the chance of survival. Many patients are willing to trade an early increased hazard for a later improved chance of a good outcome.[17] These results are reassuring for patients considering the treatment and for clinicians who have expressed concerns about the benefit of alteplase on the basis of previously published estimates of its effect on survival.[3,5] Although the effect on survival after the first 7 days is modest, it adds weight to the existing evidence for the long-term benefits of alteplase on functional outcome and quality of life,[9] and so reinforces the case for thrombolytic treatment.

The improved survival beyond the acute phase can probably be explained by the effect on brain ischaemia of alteplase given within 6 h of stroke onset. Alteplase improves functional outcome at 3–6 months,[11,12] and these improvements in functional outcome could plausibly translate into survival benefits over time, as indicated by findings from other studies.[11,12] In line with this theory, the primary IST-3 analysis found that the early increase in deaths was offset by a later reduction so that, by 6 months, the numbers of deaths were similar in the two groups.[7] Our subsequent analyses of survival up to 18 months did not show a significant overall survival benefit from alteplase,[9,10] but our reanalysis of survival beyond 7 days in these datasets obtained HRs that are broadly similar to those in this 3 year follow-up analysis (appendix pp 4–5). An alternative explanation for the increased survival after the acute phase might be that participants in the alteplase plus standard care group who survived the first week were younger or had less severe stroke than participants in the standard care alone group (because older participants and those with severe stroke might have died from intracranial haemorrhage), but we found no evidence of any differences to support this hypothesis and, in any case, our analysis of survival beyond 7 days was adjusted for age and baseline stroke severity. We can therefore reasonably infer that the increased survival beyond the acute phase is an effect of alteplase that becomes evident during long-term follow-up.

We found no evidence that the proportional effect of alteplase on survival to 3 years was dependent on age, stroke severity, or time to treatment up to 6 h. For functional outcome at 3–6 months, strong evidence exists of better effects of alteplase in patients treated early than in those treated late.[1,7] Our previous analysis of case fatality at 18 months in IST-3[10] also suggested a greater benefit of early treatment, but this effect was not found in an analysis of early deaths[18] nor in this analysis at 3 years. Reanalysis of survival beyond the acute phase also showed no subgroup differences in either of the 18 month datasets, similar to this analysis of survival up to 3 years. An explanation for the absence of effect modification by time to treatment might be that our analysis of long-term survival included fewer participants than did the analyses of functional outcome at 3–6 months,[1,7] which will have affected statistical power for subgroup analyses. Additionally, at baseline, participants in our analysis were older, had more severe strokes, and were treated earlier than other participants in IST-3, which could also have restricted the scope for effect modifications to be detected. An alternative explanation might be that differences between subgroups might become attenuated with time, so that differences that were present at 3–6 months can no longer be detected at 3 years.

The main strength of this analysis is the randomisation of a large number of participants, with complete and masked recording of deaths over a long period of time. The survival analysis also accounted for the non-proportionality of hazards and provided period-specific HRs, and adjusted for key prognostic variables. Additionally, the core IST-3 dataset (with 6 month and 18 month data) was made available by April 15, 2016, through a controlled access process,[19] and publication of the dataset from this study will in due course be considered by the IST-3 publication committee.[20]

This follow-up study has some limitations. First, we were not able to follow the entire IST-3 population up to 3 years and we have therefore analysed a prespecified subgroup. However, we stratified randomisation by region and, using a minimisation algorithm, achieved a good balance between treatment groups for the known important prognostic factors. Second, the sample size was small (by comparison with the large-scale trials of thrombolytic treatment for myocardial infarction[21,22]), so the statistical power to detect moderate but worthwhile differences in case fatality was low, as was that to detect subgroup interactions. Third, participants in this analysis were somewhat older, had more severe strokes, and were randomised a little earlier than other participants in IST-3, but the result of this analysis was not different from that of the reanalysis of survival up to 18 months among all participants in the trial.[10] Fourth, although we did not find differences in age, stroke severity, or time to treatment of 7 day survivors in the two groups, we cannot rule out the possibility of a selection bias leading to other, unmeasured differences in favour of the alteplase group. Finally, management of acute ischaemic stroke is changing rapidly, and these results will not be applicable for patients receiving complementary intra-arterial treatment.[23] However, intravenous alteplase is likely to remain the primary treatment for patients without large artery occlusions and in other cases when intra-arterial treatment cannot be given, so the results will be applicable to many patients with acute ischaemic stroke worldwide for some time to come.

Although alteplase given within 6 h of ischaemic stroke was not associated with a clear reduction in the risk of death at 3 years, among participants surviving the acute phase, we noted a significant long-term survival advantage. The results of this study are reassuring for clinicians concerned about the effect of alteplase on patient survival, and will help clinicians to inform patients and their relatives, and to discuss with them the early hazards and long-term benefits of treatment.

Contributors

EB wrote the first draft of the manuscript. GC did the analyses and commented on the manuscript. WNW, MBR, and PAGS interpreted the analyses, wrote the first draft of the abstract, and commented on the manuscript. EL, A-SR, EI, JF, JS, JD, JMW, RIL, and KBS commented on the manuscript.

Declaration of interests

PAGS and JMW have received support from the Medical Research Council, the Stroke Association, the Health Foundation, and Boehringer Ingelheim. RIL has received support from Boehringer Ingelheim, Pfizer, and Covidien. KBS is employed by the Norwegian Medicines Agency and is a member of the European Medicines Agency's Committee for Medicinal Products for Human Use and Cardiovascular Working Party. All other authors declare no competing interests.

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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Berge E, Cohen G, Roaldsen MB, et al, for the IST-3 Collaborative Group. Effects of alteplase on survival after ischaemic stroke (IST-3): 3 year follow-up of a randomised, controlled, open-label trial . *Lancet Neurol* 2016; published online July 19. http://dx.doi.org/10.1016/S1474-4422(16)30139-9.

Supplementary Material

Supplementary Table 1. Causes of death within 7 days and after 7 days

	Alteplase and standard care (n=967)	**Standard care alone (n=979)**
Within 7 days		
Intracranial haemorrhage	35 (35.4)	3 (4.6)
Swelling of original infarct	30 (30.3)	14 (21.5)
Index stroke	24 (24.2)	36 (55.4)
Recurrent ischaemic stroke	0	1 (1.5)
Recurrent stroke of unknown type	1 (1.0)	0
Non-cerebral event	9 (9.1)	11 (16.9)
Total	99 (100.0)	65 (100.0)
After 7 days		
Cerebrovascular cause	92 (26.0)	114 26.6)
Cardiovascular cause	33 (9.3)	64 (14.9)
Infection	94 (26.6)	126 (29.4)
Cancer	15 (4.2)	19 (4.4)
Multiple causes	12 (3.4)	5 (1.2)
Other cause	24 (6.8)	28 (6.5)
Unknown cause	84 (23.7)	73 (17.0)
Total	354 (100.0)	429 (100.0)

Numbers are n (%)

Supplementary Table 2. Baseline characteristic by vital status at 7 days

	Alteplase and standard care (n=967)			**Standard care alone (n=979)**		
	Dead ≤7 days (n=99)	**Alive >7 days** (n=868)	**p***	**Dead ≤7 days** (n=65)	**Alive >7 days** (n=914)	**p***
Age (years)	81 (74-87)	82 (73-86)	0.49	83 (74-88)	82 (72-86)	0.19
National Institutes of Health Stroke Scale score	19 (11-24)	11 (6-17)	<0.0001	19 (14-22)	11 (6-17)	<0.0001
Time to randomisation (hours)	3.6 (2.5-4.5)	3.8 (2.8-4.8)	0.076	3.5 (2.5-4.5)	3.7 (2.8-4.7)	0.17

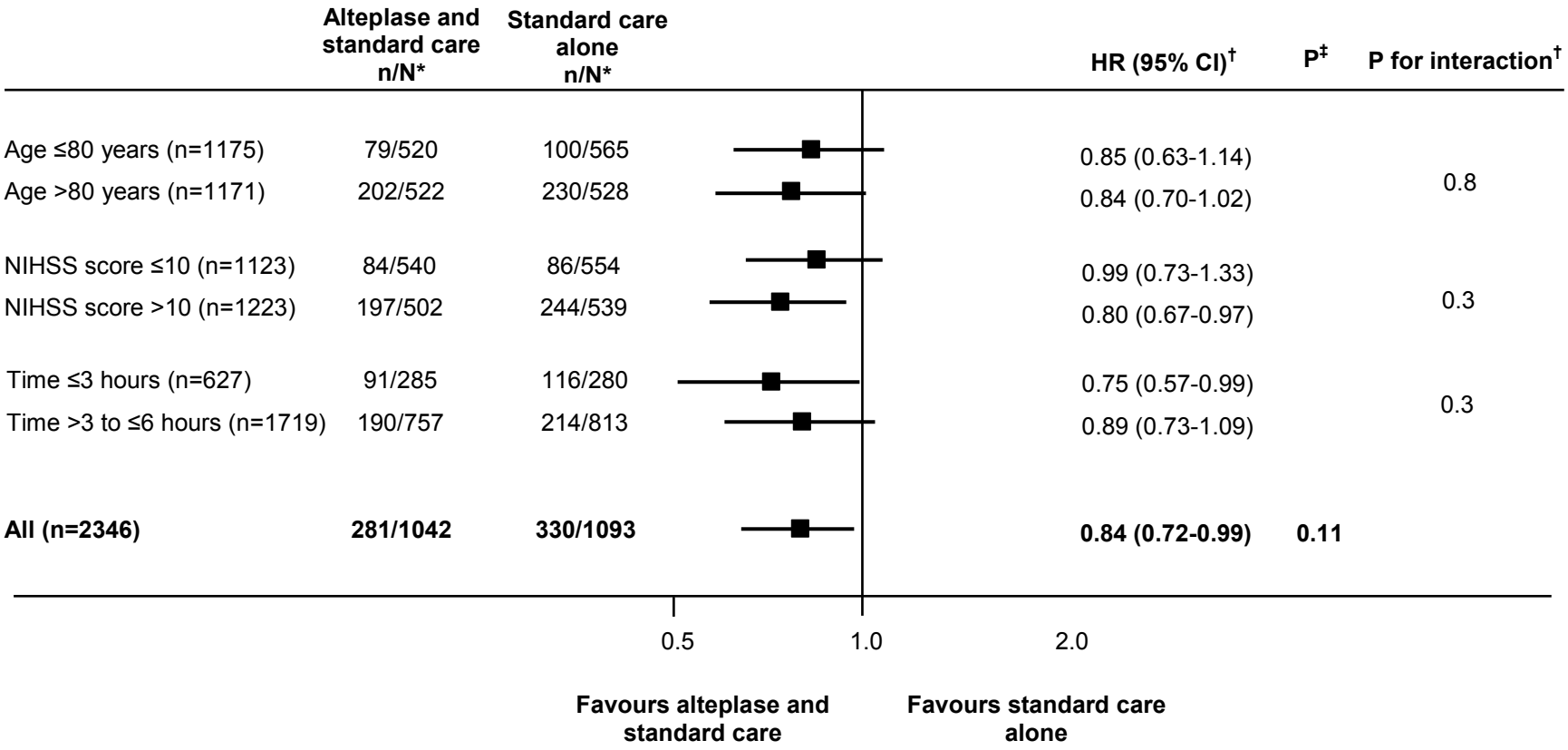
Data are median (interquartile range). *Analysis by Wilcoxon test

Supplementary Table 3. Baseline characteristics of patients from the UK and Scandinavia, and from other countries in IST-3

	UK and Scandinavia (N=1946)	**Other countries (N=1087)**
Age (years)	82 (73-86)	79 (69-84)
Female sex	999 (51.3)	570 (52.4)
National Institutes of Health Stroke Scale score	11 (7-18)	10 (5-17)
Systolic blood pressure (mm Hg)	156 (140-173)	154 (140-170)
Atrial fibrillation	613 (31.5)	300 (27.6)
Time to randomisation (hours)	3.7 (2.8-4.7)	4.1 (3.2-5.0)
Stroke syndrome		
Total anterior circulation syndrome	920 (47.3)	385 (35.4)
Partial anterior circulation syndrome	690 (35.5)	455 (41.9)
Posterior circulation syndrome	137 (7.0)	109 (10.0)
Lacunar syndrome	197 (10.1)	135 (12.4)
Infarct size		
No infarct visible	1150 (59.1)	655 (61.2)
Small/medium	464 (23.9)	231 (21.6)
Large/very large	331 (17.1)	184 (17.2)

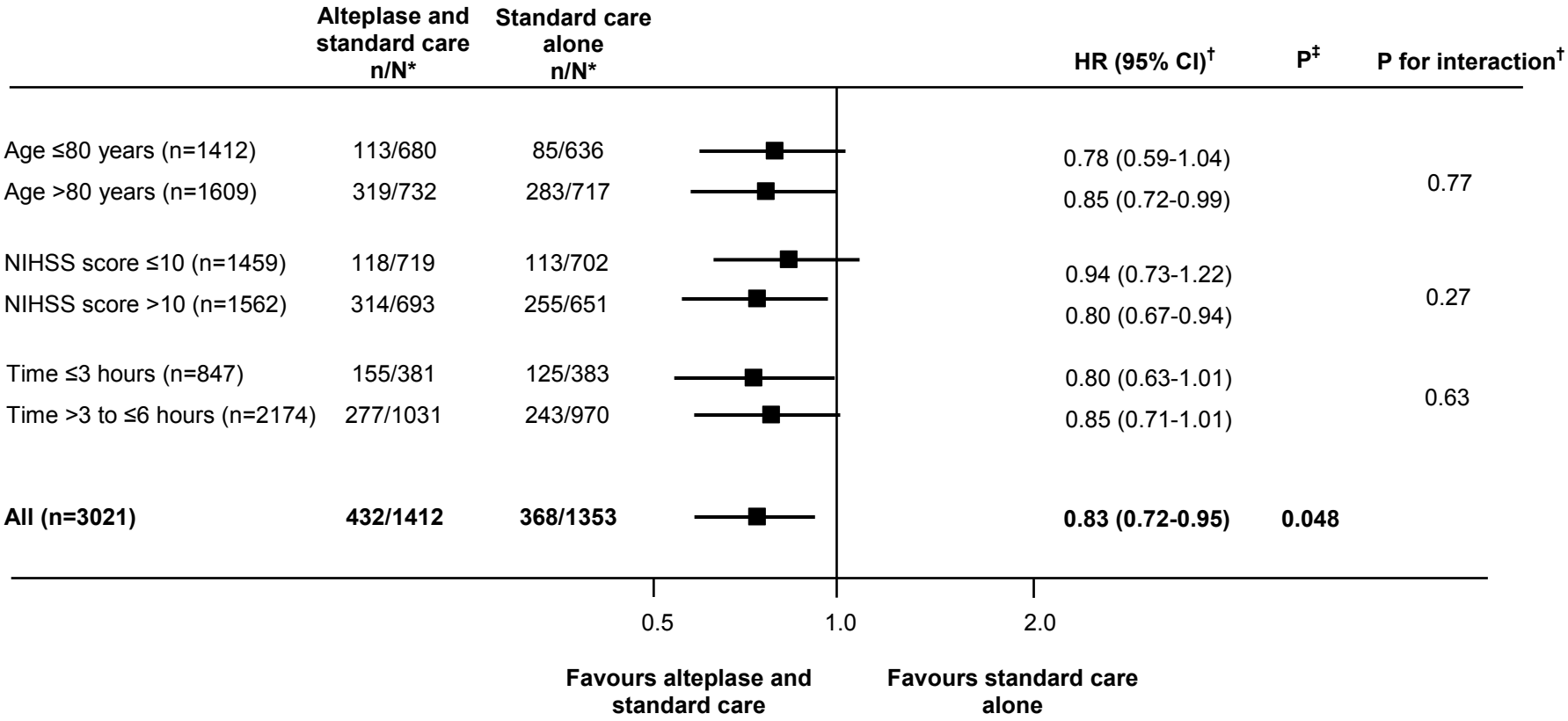
Data are median (interquartile range) or n (%). Two participants from UK/Scandinavia randomised after 6 hours excluded from analysis. One participant from UK/Scandinavia and 17 from other countries had missing values for infarct size.

Supplementary Figure 1. Hazard ratios for death from 8 days to 18 months in 2348 participants scheduled for 18 months' follow-up. Survival from 0 days to 18 months was reported in (9).



Two participants randomised after 6 h excluded from the analysis. HR Hazard ratio. NIHSS National Institutes of Health Stroke Scale. *n/N is number of patients who died during 8 days to 18 months divided by number of patients alive at 8 days. †From Cox regression analysis, adjusted for age, NIHSS score, and time to randomisation. ‡From log-rank test of difference in survival.

Supplementary Figure 2. Hazard ratios for death from 8 days to 18 months in all 3035 participants recruited into IST-3. Survival from 0 days to 18 months was reported in (10).



14 participants excluded from the analysis (1 with missing survival data, 11 with zero survival, 2 randomised after 6 h). The analysis used slightly different censoring definitions than those used in (10). HR Hazard ratio. NIHSS National Institutes of Health Stroke Scale. *n/N is number of patients who died during 8 days to 18 months divided by number of patients alive at 8 days. †From Cox regression analysis, adjusted for age, NIHSS score, and time to randomisation. ‡From log-rank test of difference in survival

Paper II

Roaldsen MB, Jusufovic M, Berge E, Lindekleiv H

Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke

Cochrane Database of Systematic Reviews 2021; 6(6): CD007574

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Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke (Review)

Roaldsen MB, Jusufovic M, Berge E, Lindekleiv H

Roaldsen MB, Jusufovic M, Berge E, Lindekleiv H.
Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke.
Cochrane Database of Systematic Reviews 2021, Issue 6. Art. No.: CD007574.
DOI: 10.1002/14651858.CD007574.pub3.

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[Intervention Review]

Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke

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ABSTRACT

Background

Most disabling strokes are due to a blockage of a large artery in the brain by a blood clot. Prompt removal of the clot with intra-arterial thrombolytic drugs or mechanical devices, or both, can restore blood flow before major brain damage has occurred, leading to improved recovery. However, these so-called endovascular interventions can cause bleeding in the brain. This is a review of randomised controlled trials of endovascular thrombectomy or intra-arterial thrombolysis, or both, for acute ischaemic stroke.

Objectives

To assess whether endovascular thrombectomy or intra-arterial interventions, or both, plus medical treatment are superior to medical treatment alone in people with acute ischaemic stroke.

Search methods

We searched the Trials Registers of the Cochrane Stroke Group and Cochrane Vascular Group (last searched 1 September 2020), CENTRAL (the Cochrane Library, 1 September 2020), MEDLINE (May 2010 to 1 September 2020), and Embase (May 2010 to 1 September 2020). We also searched trials registers, screened reference lists, and contacted researchers.

Selection criteria

Randomised controlled trials (RCTs) of any endovascular intervention plus medical treatment compared with medical treatment alone in people with definite ischaemic stroke.

Data collection and analysis

Two review authors (MBR and MJ) applied the inclusion criteria, extracted data, and assessed trial quality. Two review authors (MBR and HL) assessed risk of bias, and the certainty of the evidence using GRADE. We obtained both published and unpublished data if available. Our primary outcome was favourable functional outcome at the end of the scheduled follow-up period, defined as a modified Rankin Scale score of 0 to 2. Eighteen trials (i.e. all but one included trial) reported their outcome at 90 days. Secondary outcomes were death from all causes at in the acute phase and by the end of follow-up, symptomatic intracranial haemorrhage in the acute phase and by the end of follow-up, neurological status at the end of follow-up, and degree of recanalisation.

Main results

We included 19 studies with a total of 3793 participants. The majority of participants had large artery occlusion in the anterior circulation, and were treated within six hours of symptom onset with endovascular thrombectomy. Treatment increased the chance of achieving a good functional outcome, defined as a modified Rankin Scale score of 0 to 2: risk ratio (RR) 1.50 (95% confidence interval (CI) 1.37 to 1.63; 3715 participants, 18 RCTs; high-certainty evidence). Treatment also reduced the risk of death at end of follow-up: RR 0.85 (95% CI 0.75 to 0.97; 3793 participants, 19 RCTs; high-certainty evidence) without increasing the risk of symptomatic intracranial haemorrhage in the acute phase: RR 1.46 (95% CI 0.91 to 2.36; 1559 participants, 6 RCTs; high-certainty evidence) or by end of follow-up: RR 1.05 (95% CI 0.72 to 1.52; 1752 participants, 10 RCTs; high-certainty evidence); however, the wide confidence intervals preclude any firm conclusion. Neurological recovery to National Institutes of Health Stroke Scale (NIHSS) score 0 to 1 and degree of recanalisation rates were better in the treatment group: RR 2.03 (95% CI 1.21 to 3.40; 334 participants, 3 RCTs; moderate-certainty evidence) and RR 8.25 (95% CI 1.63 to 41.90; 198 participants, 2 RCTs; moderate-certainty evidence), respectively.

Authors' conclusions

In individuals with acute ischaemic stroke due to large artery occlusion in the anterior circulation, endovascular thrombectomy can increase the chance of survival with a good functional outcome without increasing the risk of intracerebral haemorrhage or death.

PLAIN LANGUAGE SUMMARY

Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke

Review question

This review addressed whether endovascular thrombectomy (removal of a blood clot in a blood vessel using a mechanical device) or intra-arterial thrombolysis (injecting clot-dissolving drugs directly into the clot), or both, provide better outcomes than standard treatment alone in stroke caused by a blocked blood vessel.

Background

The majority of disabling strokes are due to a blockage of a large blood vessel by a blood clot in the brain. Such strokes lead to brain tissue damage because of oxygen deprivation. An ischaemic stroke is a stroke where the restriction of blood flow causes damage and death to the surrounding tissue due to oxygen shortage. For these patients, the most intuitive means of treatment is removal of the blockage by either injecting clot-dissolving drugs directly into the clot or removal of the blood clot using a mechanical device, or both. Prompt treatment can restore blood flow before major brain damage has occurred, leading to a good recovery. However, these treatments can also cause bleeding in the brain, which can result in poorer outcomes. We searched for randomised controlled trials (studies in which participants are assigned to one of two or more treatment groups using a random method) of both endovascular mechanical thrombectomy and intra-arterial thrombolysis to establish whether they are safe and effective treatments for stroke caused by a blocked blood vessel.

Search date

1 September 2020

Study characteristics

Randomised controlled trials of endovascular thrombectomy or intra-arterial thrombolysis, or both, plus routine medical treatment compared with routine medical treatment alone in people with a definite acute ischaemic stroke.

Study funding sources

No funding sources.

Key results

We found 19 trials involving a total of 3793 participants. Treatment with endovascular thrombectomy can improve patients' chance of survival with the ability to function well without increasing the risk of bleeding in the brain or death. It is still unclear what the optimal time window is within which treatment is beneficial and whether treatment is effective in the posterior (supplying the rear part of the brain) circulation. There is also a need to study whether a strategy of primary endovascular thrombectomy or intra-arterial thrombolysis, or both, is superior to a strategy where intravenous (injected into the vein) clot-dissolving treatment is provided first in a local centre followed by transfer of selected patients to hospitals able to perform mechanical thrombectomy or intra-arterial thrombolysis, or both.

Certainty of the evidence

We judged the available trials to be at low or unclear risk of bias, and so overall the evidence is reported to be of high certainty.

Summary of findings 1. Endovascular thrombectomy interventions compared to standard therapy for acute ischaemic stroke

Endovascular thrombectomy interventions compared to standard therapy for acute ischaemic stroke

Patient or population: acute ischaemic stroke
Setting: hospital
Intervention: endovascular thrombectomy or intra-arterial interventions, or both
Comparison: standard therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with routine medical treatment	Risk with endovascular thrombectomy interventions			
Favourable functional outcome at the end of follow-up (primary outcome: mRS score 0 to 2) Follow-up: 90 days[a]	290 per 1000	435 per 1000 (397 to 475)	RR 1.50 (1.37 to 1.63)	3715 (18 RCTs)	⊕⊕⊕⊕ High[b]
Death from all causes at the end of follow-up Follow-up: 90 days[a]	207 per 1000	176 per 1000 (153 to 203)	RR 0.85 (0.75 to 0.97)	3793 (19 RCTs)	⊕⊕⊕⊕ High[b]
Symptomatic intracranial haemorrhage at the end of follow-up (NINDS) Follow-up: 90 days[a]	58 per 1000	58 per 1000 (37 to 88)	RR 1.05 (0.72 to 1.52)	1752 (10 RCTs)	⊕⊕⊕⊕ High[b]
Neurological status at the end of follow-up (NIHSS) Follow-up: 90 days[a]	123 per 1000	250 per 1000 (149 to 418)	RR 2.03 (1.21 to 3.40)	334 (3 RCTs)	⊕⊕⊕⊖ Moderate[b,c]
Degree of recanalisation (TIMI grade) Follow-up: End of endovascular procedure	16 per 1000	129 per 1000 (25 to 655)	RR 8.25 (1.63 to 41.90)	198 (2 RCTs)	⊕⊕⊕⊖ Moderate[b,c]

*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; **NINDS:** National Institute of Neurological Disorders and Stroke; **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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[a]All trials had 90 days follow-up with the exception of one trial of 16 patients (AUST 2005).
[b]Only one of these RCTs could be blinded for surgeons or participants due to the nature of the intervention.
[c]Downgraded for imprecision (wide confidence interval)

BACKGROUND

Acute ischaemic stroke is a major cause of death and disability worldwide (Warlow 2003). The usual mechanism is a thrombotic occlusion of a cerebral artery; intravenous thrombolytic treatment with recombinant tissue plasminogen activator (rt-PA) within 4.5 hours of stroke onset reduces disability (Wardlaw 2009), and is the routine recanalisation treatment. The rapidly developing field of interventional radiology currently offers a variety of alternative approaches to recanalisation in acute ischaemic stroke. This is a review of randomised controlled trials of endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke (O'Rourke 2010).

Description of the condition

An ischaemic stroke is caused by the disruption of blood flow due to a blood clot, which results in brain tissue damage and loss of function. Ischaemic stroke constitutes approximately 80% to 85% of all strokes.

Description of the intervention

Endovascular thrombectomy and intra-arterial techniques are recanalisation therapies where the blood clot is either removed using a mechanical device, most often stent retrievers; or thrombolytic medication is injected by intra-arterial means directly to the blood clot. We included all the following techniques.

- Angiojet aspiration
- Laser recanalisation
- Thromboaspiration (retrieval devices)
- Angioplasty
- Mechanical fragmentation of the thrombus
- Implantation of stents
- Intra-arterial thrombolysis
- Intra-arterial sonothrombolysis

How the intervention might work

The goal of endovascular thrombectomy and intra-arterial interventions is to remove or dissolve the blood clot causing the stroke symptoms, either by using a mechanical device or, in some cases, by injecting thrombolytic drugs, such as urokinase or alteplase, directly to the embolus, or by a combination of both techniques. If recanalisation is achieved, the patient's affected brain tissue can recover, and if done in time and without complications, the patient's functional outcome can be significantly improved.

Why it is important to do this review

An up-to-date review on endovascular thrombectomy and intra-arterial thrombolysis for acute ischaemic stroke is highly warranted and will clarify the efficacy and safety of these relatively new acute treatment modalities for acute ischaemic stroke, which is in rapid development and gaining considerable clinical significance in acute stroke care. Several new publications in this field are included in this updated and highly relevant review.

OBJECTIVES

To assess whether endovascular thrombectomy or intra-arterial interventions, or both, plus medical treatment are superior to medical treatment alone in people with acute ischaemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing endovascular thrombectomy and intra-arterial interventions plus medical treatment to medical treatment alone in people with definite acute ischaemic stroke. We excluded cluster randomised trials.

Types of participants

People with a definite acute ischaemic stroke (a computed tomography (CT) or magnetic resonance imaging (MRI) must have excluded cerebral haemorrhage).

Types of interventions

All endovascular thrombectomy and intra-arterial techniques aimed at revascularisation in acute ischaemic stroke, including but not limited to:

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

All types of medical treatment could be given in addition to the endovascular thrombectomy and intra-arterial techniques.

Type of comparison therapy

The comparison therapy was routine medical treatment. Intravenous thrombolytic treatment was permissible only when the same intravenous thrombolytic treatment was also given to the intervention group.

Types of outcome measures

Primary outcomes

Favourable functional outcome at the end of the scheduled follow-up period defined as a modified Rankin Scale (mRS) score of 0 to 2. Given that some prefer a definition of 'favourable outcome' as a score of 0 to 1 (NINDS 1995), we also sought data on the number of participants in each individual mRS category. If the mRS score was not reported, we used the trial's definition of functional outcome. Eighteen of the included trials (i.e. all but one trial: AUST 2005) reported their outcome at 90 days.

Secondary outcomes

- Death from all causes, both:
  - during the acute phase, i.e. first seven to 10 days; and
  - at the end of scheduled follow-up.

- Symptomatic intracranial haemorrhage within the acute phase (non-fatal or fatal) and at the end of follow-up. We defined symptomatic intracranial haemorrhage according to both the National Institute of Neurological Disorders and Stroke (NINDS) study (NINDS 1995), and the European Cooperative Acute Stroke Study (ECASS) criteria (Hacke 1995). When symptomatic intracranial haemorrhage was not reported according to these criteria, we used the trial's definition.
- Neurological status at the end of follow-up. We defined favourable neurological outcome as National Institutes of Health Stroke Scale (NIHSS) score 0 to 1.
- Degree of recanalisation, according to Higashida 2003, and using the Thrombolysis In Myocardial Infarction (TIMI) grade (Khatri 2005) or the Thrombolysis In Cerebral Infarction (TICI) grade.
- Major extracranial haemorrhage in the acute phase.

Search methods for identification of studies

See the methods for the Cochrane Stroke Group Specialised Register. We searched for trials in all languages and arranged for translation of trial reports where necessary.

Electronic searches

We searched the Cochrane Stroke Group Specialised Register (1 September 2020) and the Trials Register of Cochrane Vascular Group (last searched 1 September 2020). In addition, we updated the searches in the following electronic databases. (We adapted the MEDLINE search strategy for the other databases.)

- MEDLINE Ovid (from May 2010 to 1 September 2020) (Appendix 1).
- Embase Ovid (from May 2010 to 1 September 2020) (Appendix 2).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 8) in the Cochrane Library (searched 1 September 2020). (Appendix 3)
- Science Citation Index (from 1980 to 1 September 2020). (Appendix 4)

We also searched the following ongoing trials registers (last searched 1 September 2020).

- Stroke Trials Registry (www.strokecenter.org/trials).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov). (Appendix 5)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en).

Searching other resources

In an attempt to identify further published, unpublished, ongoing or planned trials, we screened reference lists of relevant trials and contacted professional organisations in neuroradiology and interventional radiology, and authors and researchers active in the field.

Data collection and analysis

Selection of studies

Randomised controlled trials comparing endovascular thrombectomy and intra-arterial interventions plus medical treatment versus medical treatment alone in people with acute ischaemic stroke. Two review authors (MBR and MJ) screened the titles and abstracts of references identified by the searches. We obtained full-paper copies of those trial reports which appeared to be eligible for inclusion based on the title and abstract. Two review authors (MBR and MJ) then assessed these for inclusion in the review. Any disagreements between the authors were resolved by discussion, with input from a third review author (HL) if needed. When a trial was excluded, we kept a record of both the report and the reason for exclusion.

Data extraction and management

Two review authors (MBR and MJ) independently extracted data from the report of each eligible trial on a specially designed data extraction form. The review authors were not blinded to journal or institution. Any disagreements between the authors were resolved by discussion, with input from a third review author (HL) if needed. We extracted the following information from each report.

- Diagnostic criteria used for acute ischaemic stroke, including whether magnetic resonance imaging (MRI) diffusion/perfusion mismatch, computed tomography (CT) angiography, or CT perfusion were used to identify eligible patients.
- Time interval from onset to randomisation.
- Time of groin puncture or initiation of intra-arterial treatment.
- Numbers of participants in each treatment group with outcome events.
- Modality of endovascular thrombectomy or intra-arterial intervention used.
- Precise form of comparison therapy used.
- Data on subgroups (NIHSS score, age, time to treatment, early ischaemic changes on CT according to the Alberta Stroke Program Early CT Score (ASPECTS), use of intravenous thrombolytic medication, and sex).

One review author (MBR) entered the data into Review Manager 5 software (Review Manager 2020). These data were checked by another review author (HL) against the hard copy data extraction forms to correct and clarify data entry errors. When any relevant data were missing from the available publications, we contacted the principal investigators or industrial sponsors concerned.

Assessment of risk of bias in included studies

Two review authors (MBR and HL) performed risk of bias assessment of all the included studies using Cochrane's risk of bias tool.

Quality assessment

Two review authors (MBR and HL) independently performed quality assessment of reports of eligible trials, resolving any disagreements by discussion. We used the following criteria to assess the quality of reports of eligible trials, according to Section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- adequate sequence generation;
- allocation concealment;
- blinding: in trials of endovascular thrombectomy it is not possible to blind either the participants or those administering the interventions. However, outcome assessors can be blinded. We defined blinding as 'yes', 'no', or 'unclear' as it pertained to blinding of outcome assessors;

- incomplete outcome data addressed: we considered intention-to-treat analysis (ITT) adequate when:
  * participants were analysed in the groups to which they had been randomised irrespective of the treatment they received; and
  * when the numbers of participants lost to follow-up and the associated reasons were reported.
- free of selective reporting;
- free of other bias.

We used the above criteria to construct a risk of bias table for each eligible trial, as outlined in Section 8.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

We expressed the treatment effects of dichotomous outcomes as risk ratios with 95% confidence intervals (CI). We did not plan to include continuous outcomes.

Unit of analysis issues

The unit of analysis was the participant with acute ischaemic stroke. We excluded crossover trials; due to the nature of the disease and intervention, crossover trials are not possible.

Dealing with missing data

We contacted study authors for missing data. Where possible, ITT analysis was applied. In reporting adverse events, we assumed the 'worst case' to avoid under-reporting.

Assessment of heterogeneity

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 estimated heterogeneity between trials' results using the I^2 statistic (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 rather included an overall evaluation of the data.

Assessment of reporting biases

We undertook extensive literature searching without restrictions on publication date or language in order to limit reporting bias. We used study protocols and trial registrations to assess studies for selective reporting.

Data synthesis

We analysed the data using Review Manager 5 software (Review Manager 2020). Two review authors (MBR and HL) conducted the data analysis. The appropriate statistical analysis was a binary logistic regression. We selected the Mantel-Haenszel method.

We derived risk ratios and 95% CI for each study. We combined the results of the included studies for each outcome where appropriate. We used a fixed-effect model for pooled data and considered not pooling data if we encountered considerable heterogeneity (I^2 value of 80% or more) across studies. We performed subgroup analyses using the methodology described by Deeks and colleagues (Deeks 2001), as recommended in Section 10.11.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses and investigation of heterogeneity (via meta-regression) a priori on the following characteristics.

- Age
- Sex
- Stroke severity
- Early ischaemic changes on CT according ASPECTS
- Mean time to groin puncture or initiation of intra-arterial treatment
- Intravenous thrombolytic medication
- Intra-arterial intervention
- Localisation of cerebral artery occlusion
- Localisation of occlusion

After reviewing the articles, we amended the subgroups to include:

- intra-arterial treatment with and without mechanical thrombectomy;
- penumbra imaging in selecting patients to treatment.

We defined subgroups by age (younger and older participants, using trial definition); sex; stroke severity (according to the NIHSS score, using each trial's cutoff for severe stroke); presence of large infarction on CT (according to ASPECTS, using each trial's cutoff for large infarction), and use of intravenous thrombolytic medication. We compared trials where the mean or median time between stroke onset and initiation of intra-arterial treatment was shorter (< 250 minutes), medium (250 to 300 minutes), or longer (> 300 minutes). We compared trials that included patients with proximal occlusion only and trials of patients with both proximal and non-proximal occlusion. We compared trials where a majority of participants were treated with no mechanical device; trials where a majority of participants were treated with first-generation mechanical devices (i.e. Merci and Penumbra systems); and trials where a majority of participants were treated with stent retrievers. We compared trials that included intra-arterial treatments without mechanical thrombectomy, trials that included both intra-arterial treatments with and without mechanical thrombectomy, and trials that included patients treated with mechanical thrombectomy alone. We also compared trials that used and did not use penumbra imaging for selecting patients to treatment.

Sensitivity analysis

We conducted sensitivity analysis to compare trials included in the previous version of the review and trials identified in the current review. We also compared trials that included all planned participants versus trials that were stopped early. The sensitivity

analysis only examined the primary outcome (mRS 0 to 2, or mRS 0 to 1 if data were not available for mRS 0 to 2).

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

Summary of findings and assessment of the certainty of the evidence

We used GRADE when creating the summary of findings table. We summarised the findings in Summary of findings 1 using the GRADE approach as described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We included the following outcomes in the summary of findings table.

- Favourable functional outcome at the end of follow-up
- Death from all causes in the acute phase and at the end of follow-up
- Symptomatic intracranial haemorrhage in the acute phase and at the end of follow-up
- Neurological status at end of follow-up
- Degree of recanalisation

We planned to downgrade the certainty of evidence based on the five GRADE domains (study limitations, imprecision, inconsistency, indirectness, and publication bias) where required and to justify all decisions to downgrade the certainty of evidence.

RESULTS

Description of studies

We included 19 studies involving a total of 3793 participants randomised to either endovascular thrombectomy or intra-arterial interventions, or a combination of these two endovascular treatments, or control (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). This review update includes 15 new RCTs. The previous version included four trials with 350 participants (AUST 2005; MELT 2007; PROACT 1 1998; PROACT 2 1999). There was no statistically significant heterogeneity between the trials included in this review, therefore we deemed a fixed-effect meta-analysis to be appropriate. A total of 20 participants were lost to follow-up across all 19 studies.

Types and severities of strokes

Three studies included participants with middle cerebral artery territory strokes (MELT 2007; PROACT 1 1998; PROACT 2 1999). AUST 2005 and BEST 2019 included participants with posterior circulation strokes. MR RESCUE 2013 included participants with large-vessel, anterior circulation strokes. EASI 2017, IMS III 2013, and THRACE 2016 included participants with both anterior and posterior circulation strokes. THERAPY 2016 included participants with large vessel ischaemic stroke because of a thrombus length of over 8 mm in the anterior circulation. Eight trials included participants with proximal artery occlusion strokes in the anterior circulation (BEST 2019; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; PISTE 2016; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015). DAWN 2018 and DEFUSE 2018 included participants with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery. DAWN 2018 included participants in the extended time window from six up to 24 hours after last known to be well. DEFUSE 2018 included participants in the extended time window from six to 16 hours after last known to be well. See Characteristics of included studies table.

Age and gender of participants

One study included participants aged 18 to 75 years (MELT 2007). Eight studies included participants aged 18 to 80/85 years (AUST 2005; IMS III 2013; MR RESCUE 2013; PROACT 1 1998; PROACT 2 1999; REVASCAT 2015; THERAPY 2016; THRACE 2016). Seven studies included participants from age 18 years without any upper age limit (BEST 2019; DAWN 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; RESILIENT 2020). One study included participants aged 18 to 90 years (DEFUSE 2018).

Mean ages of participants were as follows.

- 64 years (AUST 2005; PROACT 2 1999).
- 65 years (MR CLEAN 2015; MR RESCUE 2013; SWIFT PRIME 2015).
- 66 years (REVASCAT 2015).
- 67 years (MELT 2007; PROACT 1 1998).
- 69 years (EXTEND-IA 2015; IMS III 2013).

The median age of participants in ESCAPE 2015 was 70 years. There was no age imbalance between the intervention and control groups in any of the trials.

Of participants in all 19 included studies, 1093 of 2052 (53%) in the intervention group were men and 941 of 1761 (53%) in the control group were men, so overall there was no significant sex imbalance. There were gender imbalances in six studies (AUST 2005; BEST 2019; PROACT 1 1998; PROACT 2 1999; SWIFT PRIME 2015; THERAPY 2016).

Medical history of participants

For information on the medical backgrounds of participants, see Characteristics of included studies. There were small imbalances for diabetes mellitus in PROACT 2 1999, congestive heart failure in MR RESCUE 2013, and coronary heart disease in IMS III 2013. In eight studies conventional vascular risk factors were well balanced amongst the treatment and control groups (AUST 2005; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MR CLEAN 2015; PISTE 2016; REVASCAT 2015; SWIFT PRIME 2015).

Stroke mechanism

The predominant mechanism of stroke in the included studies was classified as cardioembolism, followed by carotid atheroembolism and unknown mechanism. Lacunar infarcts were not excluded. The proportion of cardioembolic strokes ranged from around 50% in EXTEND-IA 2015 to around 85% in MELT 2007. Fourteen studies did not provide data on stroke mechanism (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; IMS III 2013; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016).

Findings on CT or MRI at randomisation

In PROACT 1 1998 and PROACT 2 1999, most participants had early ischaemic changes on CT, and a minority of participants in these two studies (8%) had ischaemic changes comprising more than one-third of the middle cerebral artery territory. Patients were not excluded from AUST 2005 on the basis of baseline ischaemic CT abnormalities, and in MELT 2007 patients with CT abnormalities

consistent with subtle early ischaemia in the insular cortex, frontal and temporal opercula, or lenticular nuclei were included.

In MR RESCUE 2013, participants were randomised based on the presence or absence of penumbra on CT or MRI. In MR CLEAN 2015, patients were included if a proximal arterial occlusion in the anterior cerebral circulation was confirmed on CT angiography, MRI angiography, or digital subtraction angiography. In ESCAPE 2015, patients were included if an occluded proximal occlusion was observed on CT angiography. Patients with large early ischaemic changes on plain CT (defined as ASPECTS ≤ 5) were excluded. In EXTEND-IA 2015, patients were included if CT angiography showed occluded internal carotid or middle cerebral artery, and there was evidence of ischaemic penumbra on CT perfusion. In SWIFT PRIME 2015, patients were included if CT angiography showed occlusion of the internal carotid or first segment of the middle cerebral artery, and there was evidence of an ischaemic penumbra on CT perfusion. In REVASCAT 2015, patients with large infarction cores (defined as ASPECTS < 7 on CT or < 6 on MRI) were excluded. In IMS III 2013, plain CT and neurological deficits were used to include patients who had an 80% likelihood of proximal occlusion strokes. The trial was amended after 284 participants were randomised to allow the use of CT angiography to identify patients with proximal occlusion strokes. In PISTE 2016, patients were enrolled if CT or MR angiography identified occlusion of the internal carotid, M1 or single proximal M2. In DEFUSE 2018, patients were included if CT perfusion or MRI diffusion and perfusion scans showed an initial infarct volume (ischaemic core) of less than 70 mL, a ratio of volume of ischaemic tissue to initial infarct volume of 1.8 or more, and an absolute volume of potentially reversible ischaemia (penumbra) of 15 mL or more. In THERAPY 2016, CT angiography was required to confirm intracranial occlusion and to rule out tandem cervical occlusion that would prevent thrombectomy without treatment. Enhanced thin-section CT scan was also used to demonstrate over 8-millimetre clot length. However, advanced perfusion imaging selection or multiphase CT or CT angiography was not required. In DAWN 2018, patients were eligible for inclusion in the trial if they had evidence of occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both, on CT angiography or magnetic resonance angiography. In THRACE 2016, occlusions had to be confirmed by CT or magnetic resonance angiography. In EASI 2017, all suspected or proven occlusions of the M1 or M2 segments of the middle cerebral artery, supraclinoid internal carotid artery, or basilar artery were included. Vascular imaging was not mandated in the protocol. In BEST 2019, patients were eligible for inclusion if they had occlusion of the basilar artery confirmed by CT angiography, MRI, or digital subtraction angiography. Patients with occlusion of the distal intracranial vertebral artery (V4 segment) resulting in no flow to the basilar artery were also included. No evidence of intracranial haemorrhage, significant cerebellar mass effect, acute hydrocephalus, or extensive bilateral brainstem ischaemia should be found on CT or MRI. In RESILIENT 2020, patients were eligible for inclusion in the study if they had an occlusion involving the intracranial internal carotid artery, the first segment of the middle cerebral artery (M1), or both. The main imaging exclusion criteria were evidence of recent intracranial haemorrhage; the presence of a large infarct, as defined by ASPECTS < 6 on CT or < 5 on diffusion weighted MRI; and the complete absence of leptomeningeal collaterals on CT angiography. If CT or MRI perfusion was performed, participants had to have a baseline infarct volume of less than 70 mL, a ratio of volume of ischaemic tissue to baseline infarct volume of 1.8 or more, and an absolute volume of potentially reversible ischaemia (penumbra) of 15 mL or more.

Time to randomisation

The protocol-defined time between onset of stroke and inclusion in the trial varied from three to 24 hours. One trial included participants up to three hours after stroke onset (IMS III 2013); two trials included participants up to 4.5 hours after stroke onset (EXTEND-IA 2015; THERAPY 2016); two trials included participants up to five hours after stroke onset (EASI 2017; THRACE 2016); six trials included participants up to six hours after stroke onset (MELT 2007; MR CLEAN 2015; PISTE 2016; PROACT 1 1998; PROACT 2 1999; SWIFT PRIME 2015); four trials included participants up to eight hours after stroke onset (BEST 2019; MR RESCUE 2013; RESILIENT 2020; REVASCAT 2015); one trial included participants up to 12 hours after stroke onset (ESCAPE 2015); one trial included participants from six to 16 hours after last to be known well (DEFUSE 2018); and two trials included participants up to 24 hours after stroke onset (AUST 2005; DAWN 2018).

The actual times to randomisation or start of therapy were variably reported. Time to randomisation was not reported in PROACT 1 1998. The time to actual delivery of endovascular thrombectomy (not start of procedure) in PROACT 1 1998 was a median 5.4 hours for the treatment group and 5.7 hours for the control group. In PROACT 2 1999, the time to randomisation was a median 4.7 hours in the treatment group and 5.1 hours in the control group. In AUST 2005, the onset to treatment time was a mean 11.8 hours in the treatment group and 12.5 hours in the control group. In MELT 2007, the onset to randomisation time was a mean 3.3 hours in the treatment group and 3.4 hours in the control group. In MR RESCUE 2013, the onset to randomisation time was 5.3 hours in the treatment group and 5.8 hours in the control group. In SWIFT PRIME 2015, the onset to randomisation time was three hours in both groups. In MR CLEAN 2015, the onset to randomisation time was 3.4 hours in both groups. In ESCAPE 2015 and REVASCAT 2015, the onset to randomisation time was 2.8 hours in both groups. The onset to randomisation time was not reported in EXTEND-IA 2015 and IMS III 2013. In IMS III 2013, the time to actual delivery of endovascular thrombectomy or intravenous thrombolytic therapy (not start of procedure) was 4.2 hours in the treatment group. In EXTEND-IA 2015, the median time from stroke onset to groin puncture was 3.5 hours in the treatment group. In DAWN 2018, the median time interval between the time that the participant was last known to be well and randomisation was 12.2 hours in the treatment group. In THERAPY 2016, stroke onset to randomisation time was reported as 181 minutes. In EASI 2017, time from stroke onset to randomisation was not reported, but the authors reported that 50% of participants in the treatment group were randomised within three hours of stroke onset. In THRACE 2016, time from stroke onset to randomisation was a median 168 minutes in the treatment group. In DEFUSE 2018, median time from stroke onset to randomisation was 10 hours and 53 minutes in the treatment group.

Participants in nine studies, ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016, were randomised earlier than participants in six studies (AUST 2005; DAWN 2018; DEFUSE 2018; MR RESCUE 2013; PROACT 1 1998; PROACT 2 1999).

Method of recanalisation

Four trials tested only intra-arterial interventions with either the drug urokinase or pro-urokinase to achieve thrombolysis (AUST 2005; MELT 2007; PROACT 1 1998; PROACT 2 1999). There were differences between these trials in dose, form, and method of drug delivery. See Characteristics of included studies table. No participants in these four studies were given intravenous thrombolytic treatment (AUST 2005; MELT 2007; PROACT 1 1998; PROACT 2 1999).

Five trials approved the use of both mechanical thrombectomy and intra-arterial interventions (BEST 2019; IMS III 2013; MR CLEAN 2015; MR RESCUE 2013; THRACE 2016). In MR CLEAN 2015, intra-arterial treatment consisted of arterial catheterisation with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, or mechanical thrombectomy was performed, or both, with the method used left to the discretion of the local interventionist. In this study either alteplase at a maximum dose of 90 mg or urokinase 1,200,000 international units (IU) was used for intra-arterial thrombolysis in the case of intra-arterial treatment. In IMS III 2013, the approach used was chosen by the local neurointerventionist and encompassed receiving mechanical thrombectomy or endovascular delivery of tissue plasminogen activator (tPA) by means of microcatheter. In BEST 2019 and MR RESCUE 2013, intra-arterial interventions were approved as rescue therapy. In THRACE 2016, intra-arterial interventions of maximum 0.3 mg/kg were approved in cases of persistent distal occlusions.

Mechanical clot disruption was prohibited by the protocol in PROACT 1 1998 and did not occur in AUST 2005. The protocols of eight trials permitted use of mechanical clot disruption, either using a guidewire or by employing stents or other devices (ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; REVASCAT 2015; SWIFT PRIME 2015). In IMS III 2013 and MR RESCUE 2013, participants were primarily treated with first-generation mechanical devices (i.e. Merci and Penumbra systems). The majority of participants were treated with stent retrievers in 10 trials (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; PISTE 2016; REVASCAT 2015; SWIFT PRIME 2015). In DEFUSE 2018, any US Food and Drug Administration (FDA)-approved thrombectomy device was allowed to perform thrombectomy. In DAWN 2018, thrombectomy was performed with the use of the Trevo device, a retrievable self-expanding stent. No other devices or intra-arterial pharmacological agents were allowed. In THRACE 2016, any device on the list from the trial's regularly updated list that was also approved by the ethics committee and the French National Agency for the Safety of Medicines and Health Products could be chosen. The following devices were used: Merci, Penumbra, Catch, and Solitaire. In EASI 2017, thrombectomy was performed using an approved device according to local practice. In THERAPY 2016, aspiration thrombectomy was performed using the Penumbra system and included the Separator 3D after December 2012, and the larger-bore ACE aspiration catheter after August 2013. In RESILIENT 2020, thrombectomy was performed with the Solitaire FR stent retriever or Penumbra aspiration system. Angioplasty and stenting of the cervical internal carotid artery could be performed if necessary. Standard medical care included the use of alteplase, following the guidelines of the Brazilian Stroke Society and the American Heart Association. In BEST 2019, participants received intravenous alteplase if they met the criteria for intravenous thrombolysis within 4.5 hours of stroke symptom onset as per existing guidelines. Mechanical thrombectomy was performed with stent retriever (preferred choice) or thrombo-aspiration devices. Ten trials used only endovascular mechanical thrombectomy and no intra-arterial thrombolysis (DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; PISTE 2016; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016).

A total of 445 participants (89%) from MR CLEAN 2015, 44 participants (37%) from MR RESCUE 2013, 18 participants (10%) from DEFUSE 2018, 46 participants (60%) from EASI 2017, 150 participants (73%) from REVASCAT 2015, 18 participants (9%) from DAWN 2018, and 238 participants (75%) from EXTEND-IA 2015 were given intravenous thrombolytic treatment before randomisation. The inclusion criteria of six studies specified that all participants should be given intravenous thrombolytic treatment as a bridging to intra-arterial treatment (ESCAPE 2015; IMS III 2013; PISTE 2016; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016).

Concomitant use of antithrombotic treatment

The protocols for concomitant antithrombotic therapy varied amongst trials. There may have been an imbalance in the use of antithrombotic therapy in PROACT 1 1998, where safety concerns prompted an alteration of the concomitant antithrombotic regimen during the trial. Similarly, the MELT 2007 protocol specified that heparin, warfarin, and aspirin should not be given for 24 hours in the treatment group. In DAWN 2018, participants who had not received intravenous alteplase could receive therapy with antiplatelet agents after 24 hours postrandomisation. Standard medical care was provided in accordance with local guidelines. Ten studies did not report differences between the intervention and the control group in the use of antiplatelet or treatment with alteplase (AUST 2005; DEFUSE 2018; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MR CLEAN 2015; MR RESCUE 2013; PROACT 2 1999; REVASCAT 2015; SWIFT PRIME 2015).

There were also differences in the use of heparin. In PROACT 1 1998, participants in both the intervention and control groups received heparin. In 11 studies heparin was only given to participants in the intervention group who underwent angiography (AUST 2005; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 2 1999; REVASCAT 2015; SWIFT PRIME 2015).

Assessment of outcome

All studies reported death at the end of follow-up. Data were available for deaths in the acute phase from one study (MELT 2007). Functional outcome was assessed using the modified Rankin scale (mRS) in all included studies. All studies provided data on mRS score 0 to 2, with the exception of PROACT 1 1998, which only provided data on mRS score 0 to 1. All studies except AUST 2005 collected the outcomes of interest at 90 days.

The methods of determination of intracranial haemorrhage varied and are provided in the Characteristics of included studies table.

Nine studies reported recanalisation using the thrombolysis in cerebral infarction (TICI) or modified TICI classification (DAWN 2018; DEFUSE 2018; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; PISTE 2016; PROACT 1 1998; PROACT 2 1999; SWIFT PRIME 2015). TICI grade 3 is complete perfusion, and TICI grade 2 is partial perfusion. MELT 2007 reported recanalisation as:

1. complete;
2. partial and less than 50% in the affected territory;
3. partial and at least 50% in the affected territory; and
4. no recanalisation.

AUST 2005 did not prespecify criteria for judging recanalisation, although recanalisation at days 7 to 10 was a prespecified secondary outcome. Recanalisation was described as either complete or partial.

Results of the search

The search yielded 11,062 articles, of which four studies were included in the previous version of this review (O'Rourke 2010). A total of 57 articles were assessed as potentially eligible and retrieved in full text. We excluded 31 studies because they were not RCTs of endovascular stroke therapies. Upon closer examination of the remaining 26 studies, we excluded seven studies because they compared endovascular therapy with other therapies (such as intravenous thrombolytic treatment) and were not eligible for inclusion in the present meta-analysis (Ducrocq 2005; Keris 2001; Lewandowski 1999; Sen 2009; SYNTHESIS Expansion 2013; SYNTHESIS pilot 2010; Wolfe 2008).

We identified six ongoing studies (ISRCTN19922220; NCT01717755; NCT01852201; NCT02419781; NCT03094715; NCT03805308).

A PRISMA study flow diagram is shown in Figure 1.

Figure 1. PRISMA study flow diagram.

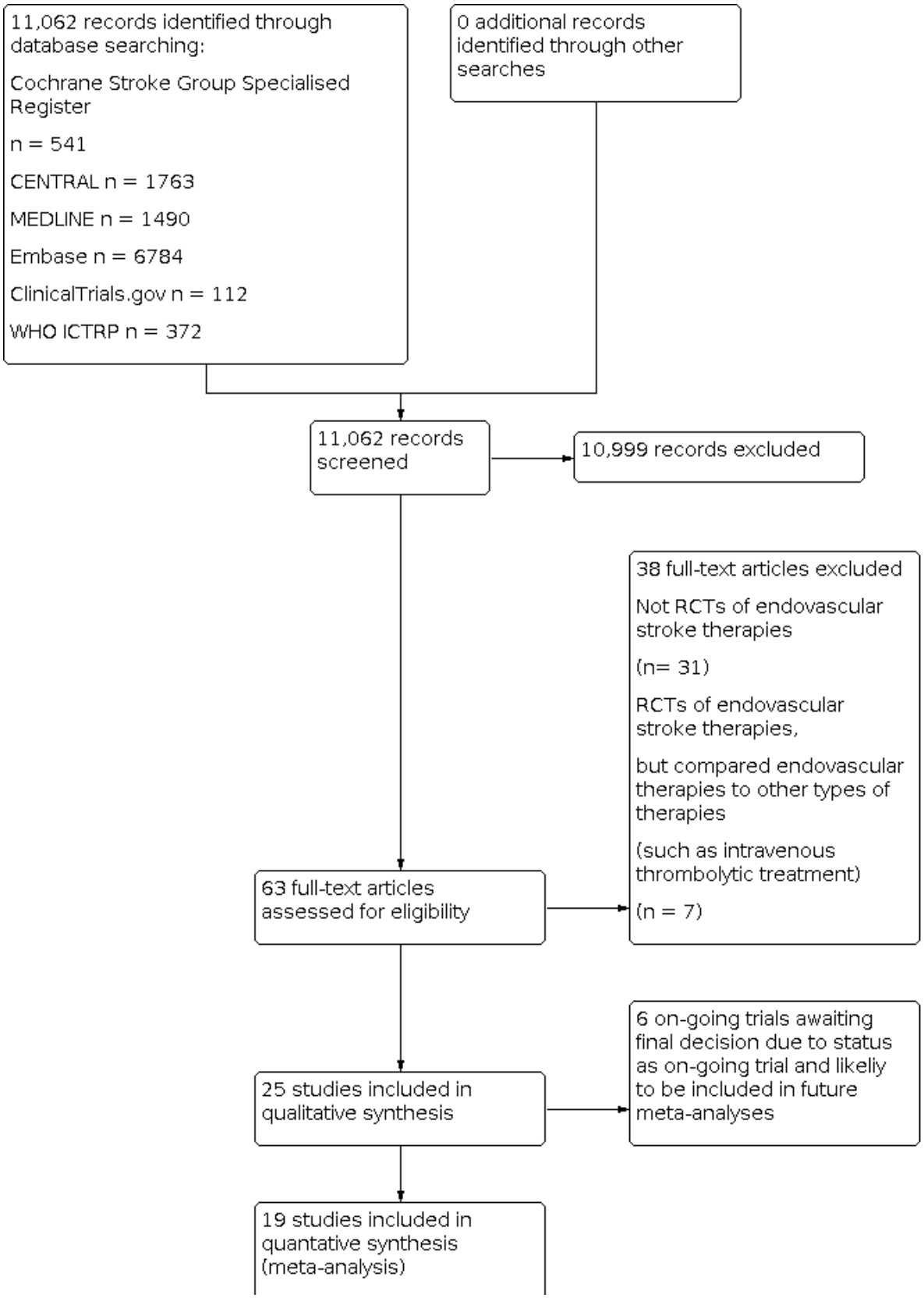
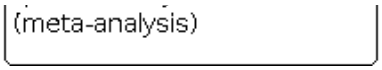


Figure 1. (Continued)



Included studies

We included 19 studies in the review (see Characteristics of included studies) (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016).

All trials except AUST 2005 collected the outcomes of interest at 90 days' follow-up.

Excluded studies

We excluded seven studies (see Characteristics of excluded studies) (Ducrocq 2005; Keris 2001; Lewandowski 1999; Sen 2009; SYNTHESIS Expansion 2013; SYNTHESIS pilot 2010; Wolfe 2008).

Risk of bias in included studies

The quality of randomisation was adequate in 15 studies (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THRACE 2016). The quality of randomisation was unclear in four studies, as the studies did not report the precise methodology of sequence generation (AUST 2005; MELT 2007; PROACT 1 1998; THERAPY 2016).

A total of 20 participants were lost to follow-up in the 19 included trials. One trial did not report ITT analyses (PROACT 1 1998), and one trial did not report on their prespecified secondary outcomes (AUST 2005).

Sixteen trials were terminated early either due to efficacy or lack of equipoise and consequently suffered from a lack of statistical power (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; PISTE 2016; PROACT 1 1998; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). For details, see Characteristics of included studies.

Allocation

The quality of randomisation was adequate in 15 studies (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THRACE 2016). The quality of randomisation was unclear in four studies, as the studies did not report the precise methodology of sequence generation (AUST 2005; MELT 2007; PROACT 1 1998; THERAPY 2016).

We assessed 16 studies as at low risk of bias (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THRACE 2016), and three studies as at unclear risk of bias (AUST 2005; EXTEND-IA 2015; THERAPY 2016).

Blinding

In only one trial (PROACT 1 1998) were the participants and personnel blinded for treatment. We assessed the other 18 studies to be of unclear risk of bias (perfomance bias) (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). Even though the nature of the intervention makes it difficult both practically and ethically to perform double-blind studies this is a source of bias. We assessed 17 studies to be at low risk of bias (detection bias) (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016), and two studies to be of high risk of bias (EASI 2017; THRACE 2016). In EASI 2017, all data and outcome measures were collected by unblinded routine care personnel, and in THRACE 2016, outcome assessment was performed by vascular neurologists not masked to the allocated treatment.

Incomplete outcome data

We assessed 13 studies as at low risk (AUST 2005; BEST 2019; DAWN 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015); four trials as at an unclear risk (DEFUSE 2018; PISTE 2016; THERAPY 2016; THRACE 2016); and two trials as at high risk of attrition bias (MR RESCUE 2013; PROACT 1 1998). MR RESCUE 2013 presented per-protocol analyses, and nine participants were excluded from the analyses (five did not have target lesion on vessel imaging; two did not have post-tPA vessel imaging; and two had failed perfusion imaging). PROACT 1 1998 did not report the primary efficacy outcome for six randomised but untreated participants (i.e. an on-treatment rather than the preferred ITT analysis). Of these six participants, five were in the treatment group, representing 16% of the total randomised treatment group; the remaining randomised but untreated participant was in the placebo group. Given the possibility that the five participants randomised to the treatment group who did not receive treatment represented a subgroup of non-responders, this may have had the effect of enriching the treatment group with responders and biasing the results in favour of treatment. The primary safety outcome was reported for these six participants, therefore we do not consider that the safety analysis was prone to on-treatment bias.

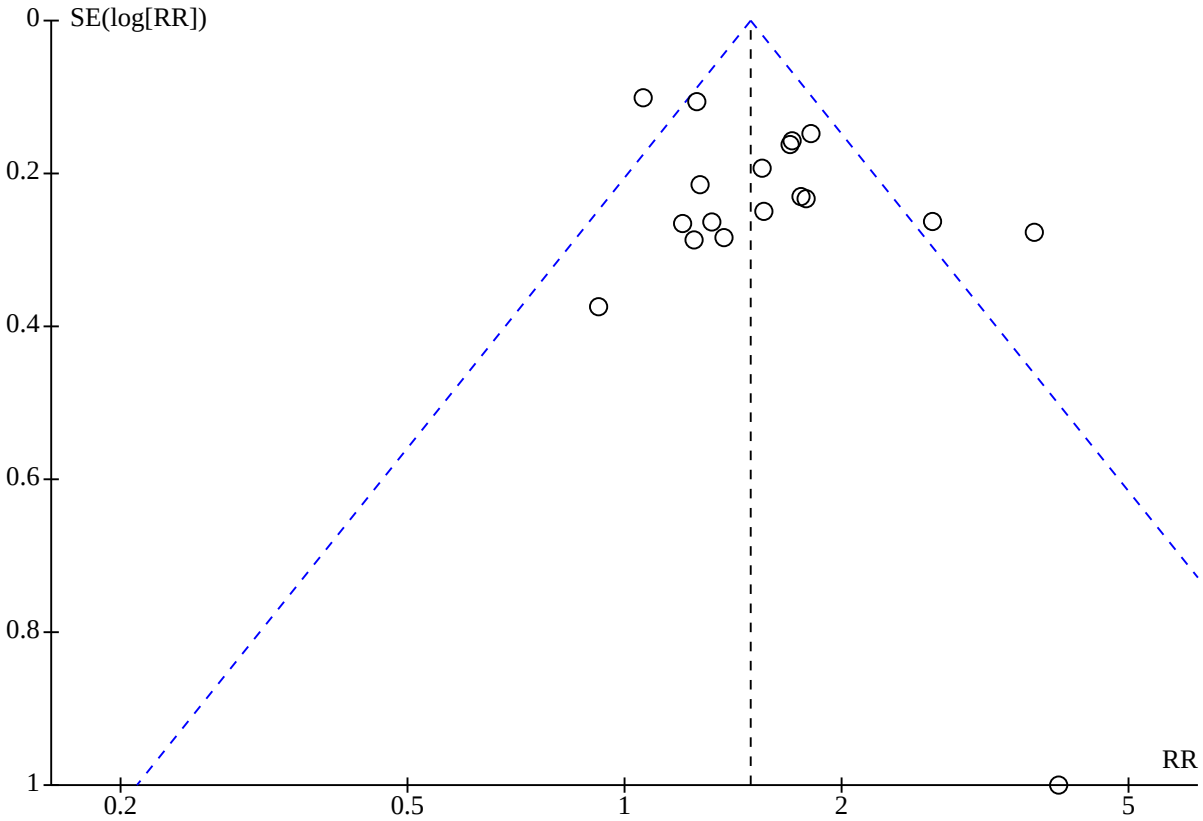
Selective reporting

Four studies were not analysed according to the ITT principle (ESCAPE 2015; PROACT 1 1998; SWIFT PRIME 2015; THERAPY 2016). We assessed 17 studies to be at low risk (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016), and one study to be at unclear risk of reporting bias (THRACE 2016). We assessed one study to be

at high risk of bias because this trial did not report prespecified secondary outcomes (AUST 2005). Baseline angiographic findings were not reported for two participants. There was no a priori requirement for follow-up imaging in this study.

We explored publication bias by inspecting the funnel plot (Figure 2). We considered the funnel plot visually symmetric.

Figure 2. Funnel plot of comparison: Favourable functional outcome at end of follow-up (functional outcome: mRS 0 to 2).



Other potential sources of bias

A total of 20 participants were lost to follow-up in the 19 included studies. Sixteen trials were terminated early either due to efficacy or lack of equipoise, and thus suffered from a lack of statistical power (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; PISTE 2016; PROACT 1 1998; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). We assessed eight studies to be at low risk (DAWN 2018; DEFUSE 2018; PISTE 2016; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016), and 11 studies to be at unclear risk of other bias (AUST 2005; BEST 2019; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PROACT 2 1999). We assessed one study to be at high risk of other bias (PROACT 1 1998). This study did not report the primary efficacy outcome for six randomised but untreated participants (i.e. an on-treatment rather than the preferred ITT analysis). Of these six participants, five were in the treatment group, representing 16% of the total randomised treatment group; the remaining randomised but untreated participant was in the placebo group. Given the possibility that the five participants randomised to the treatment group who did not receive treatment represented a subgroup of non-responders, this may have had the effect of enriching the treatment group with responders and biasing the results in favour of treatment. The primary safety outcome was reported for these six participants, therefore we do not consider that the safety analysis was prone to on-treatment bias. Any on-treatment bias due to these six participants would be diluted in the overall analysis. Also, this trial was stopped early by the sponsor to determine whether there was sufficient evidence of safety and efficacy to support continuation of a longer-term programme, which was ultimately expressed in the form of the phase III PROACT 2 1999 trial. No safety concerns were involved in that decision. An analysis of the data set from all participants who underwent angiography by a biostatistical unit independent of the conduct of the trial forms the basis of the published PROACT 1 1998 report. At the time of termination, the PROACT 1 1998 trial had achieved 89% of its target sample size. The implications are difficult to interpret. As a general principle, trials that are stopped for any reason other than according to specific predefined stopping rules are theoretically prone to bias. However, it remains unclear whether this factor introduced any bias in this particular case.

Effects of interventions

See: **Summary of findings 1** Endovascular thrombectomy interventions compared to standard therapy for acute ischaemic stroke

Favourable functional outcome at the end of follow-up

For mRS 0 to 2, data were available for a total of 3715 participants from 18 trials (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). There was overall an effect in favour of treatment (risk ratio (RR) 1.50, 95% confidence interval (CI) 1.37 to 1.63; 3715 participants, 18 RCTs; high-certainty evidence) with moderate between-study heterogeneity (I^2 = 56%) (Analysis 1.1).

For mRS 0 to 1, data were available for a total of 3632 participants from 18 trials (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). There was a high effect in favour of treatment (RR 1.61, 95% CI 1.42 to 1.82, 3632 participants, 18 RCTs) with moderate between-study heterogeneity (I^2 = 38%) (Analysis 1.2).

Death from all causes at the end of follow-up

Data were available for a total of 3793 participants from all 19 trials (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016). There was a reduced risk of death in the treatment group (RR 0.85, 95% CI 0.75 to 0.97; 3793 participants, 19 RCTs; high-certainty evidence) with little between-study heterogeneity (I^2 = 0%) (Analysis 2.1).

Death from all causes during the acute phase

Data were available for a total of 1243 participants from three trials (IMS III 2013; MELT 2007; MR CLEAN 2015). There was no evidence of an effect of treatment on deaths in the acute phase (RR 1.06, 95% CI 0.77 to 1.47; 1243 participants, 3 RCTs) with I^2 = 0% (Analysis 2.2).

Symptomatic intracranial haemorrhage during the acute phase

Data were available for a total of 1559 participants from six trials (DAWN 2018; IMS III 2013; MR RESCUE 2013; PROACT 1 1998; PROACT 2 1999; THRACE 2016). We observed no excess risk of symptomatic intracranial haemorrhage in the treatment group (RR 1.46, 95% CI 0.91 to 2.36; 1559 participants, 6 RCTs) with very little between-study heterogeneity (I^2 = 0%) (Analysis 3.1).

Symptomatic intracranial haemorrhage at the end of follow-up

Data were available for a total of 1752 participants from 10 trials (DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; PISTE 2016; PROACT 1 1998; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016). We observed no excess risk of intracranial haemorrhage in the treatment group (RR 1.05, 95% CI 0.72 to 1.52; 1752 participants, 10 RCTs; high-certainty evidence) with no between-study heterogeneity (I^2 = 0%) (Analysis 3.2).

Neurological outcome at the end of follow-up

NIHSS data were available for a total of 334 participants from three trials (MELT 2007; PROACT 1 1998; PROACT 2 1999). There was an effect in favour of treatment (RR 2.03, 95% CI 1.21 to 3.40; 334 participants, 3 RCTs; moderate-certainty evidence) with no between-study heterogeneity (I^2 = 0%) (Analysis 4.1).

Degree of recanalisation

Data on complete recanalisation (TIMI grade 3) were available for 198 participants from two trials (PROACT 1 1998; PROACT 2 1999). For TIMI grade 3, there was an overall effect in favour of treatment (RR 8.25, 95% CI 1.63 to 41.90; 198 participants, 2 RCTs; moderate-certainty evidence) with no between-study heterogeneity (I^2 = 0%) (Analysis 5.1).

Data on complete or complete or partial recanalisation (TICI grade 2 or 3) were available for 974 participants randomised to treatment from 10 trials (DAWN 2018; DEFUSE 2018; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; PISTE 2016; PROACT 1 1998; PROACT 2 1999; SWIFT PRIME 2015; THERAPY 2016), and for 99 participants randomised to control from three trials (EXTEND-IA 2015; PROACT 1 1998; PROACT 2 1999). In the three trials that provided data on TIMI 2 or 3 for both the treatment group and the controls (total 268 participants) (EXTEND-IA 2015; PROACT 1 1998; PROACT 2 1999), there was an effect in favour of treatment (RR 3.11, 95% CI 2.18 to 4.42; P < 0.00001; 268 participants, 3 RCTs) with moderate between-study heterogeneity (I^2 = 48%) Analysis 5.2.

Major extracranial haemorrhage during the acute phase

In PROACT 1 1998, two participants had severe injection site haemorrhages; however, the allocation of these participants was unclear. No participants in MELT 2007 had major extracranial haemorrhage in the acute phase. In THRACE 2016, three participants had groin haematoma, and in RESILIENT 2020, one participant in the intervention group had groin haematoma. In DAWN 2018, one participant had access-site complications leading to intervention. In ESCAPE 2015, three participants in the intervention group had haematomas at the access site. In EXTEND-IA 2015, one participant had groin/retroperitoneal haematoma and was given a blood transfusion. In MR CLEAN 2015, two participants in the control group had major extracranial haemorrhage. In REVASCAT 2015, five participants in the control group had extracranial haemorrhage. It was unclear whether any participants in the following nine studies had major extracranial haemorrhages in the acute phase: AUST 2005; BEST 2019; DEFUSE 2018; EASI 2017; IMS III 2013; MR RESCUE 2013; PROACT 2 1999; SWIFT PRIME 2015; THERAPY 2016.

Subgroup analyses

Age and sex

There was no difference in the effects of the intervention between younger and older participants in the nine trials that provided subgroup data on age (RR 1.72, 95% CI 1.48 to 2.0 versus RR 1.49, 95% CI 1.18 to 1.87; P for interaction = 0.29) (DAWN 2018; DEFUSE 2018; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THRACE 2016). The cutoff for younger and older participants varied between the trials, from 66

years in IMS III 2013 to 80 years in ESCAPE 2015 and MR CLEAN 2015 (Analysis 6.1).

There were no differences in the effects of the intervention between women and men in the seven trials that provided subgroup data on sex (RR 1.67, 95% CI 1.37 to 2.04 versus RR 1.63, 95% CI 1.34 to 1.98; P for interaction = 0.85) (Analysis 6.2) (DAWN 2018; DEFUSE 2018; ESCAPE 2015; IMS III 2013; RESILIENT 2020; SWIFT PRIME 2015; THRACE 2016).

Stroke severity

Participants with higher NIHSS scores had a better effect of the intervention than participants with lower NIHSS scores in the nine trials that provided subgroup data on NIHSS score (RR 1.42, 95% CI 1.22 to 1.66 versus RR 2.0, 95% CI 1.57 to 2.55; P for interaction = 0.02) (DAWN 2018; DEFUSE 2018; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THRACE 2016). The cutoff for NIHSS score varied from 17 to 21 (Analysis 6.3).

Early ischaemic change

There was a better effect of the intervention in participants with more pronounced early ischaemic changes on CT (lower ASPECTS) than in those with less early ischaemic changes on CT (higher ASPECTS) in the six trials that provided subgroup data on ASPECTS (RR 2.01, 95% CI 1.53 to 2.66 versus RR 1.39, 95% CI 1.19 to 1.62; P for interaction = 0.02) (ESCAPE 2015; IMS III 2013; MR CLEAN 2015; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015). The cutoff for ASPECTS varied from 7 in ESCAPE 2015 and REVASCAT 2015 to 8 in IMS III 2013, MR CLEAN 2015, and SWIFT PRIME 2015 (Analysis 6.4).

Time to intervention

There was no difference between the effect of intervention in trials with a shorter mean or median time (< 250 minutes) to start of intervention (RR 1.67, 95% CI 1.40 to 2.00) (ESCAPE 2015; EXTEND-IA 2015; MELT 2007; SWIFT PRIME 2015); medium time (250 to 300 minutes) (RR 1.30, 95% CI 1.11 to 1.51) (IMS III 2013; MR CLEAN 2015; REVASCAT 2015); and longer time (> 300 minutes) to start of intervention (RR 1.41, 95% CI 0.97 to 2.04; P for interaction = 0.10) (Analysis 6.5) (AUST 2005; MR RESCUE 2013; PROACT 1 1998; PROACT 2 1999).

Intravenous thrombolytic treatment before randomisation

There was no difference in the effect of the intervention between participants who had been given intravenous thrombolytic treatment compared to those who had not been given intravenous thrombolytic treatment before randomisation in the four trials that provided subgroup data on thrombolytic treatment (RR 1.95, 95% CI 1.55 to 2.46 versus RR 2.18, 95% CI 1.37 to 3.47; P = 0.67) (Analysis 6.6) (ESCAPE 2015; IMS III 2013; RESILIENT 2020).

Method of recanalisation

There were differences between the effect of the intervention in trials where participants were treated with intra-arterial thrombolysis alone without any endovascular mechanical thrombectomy (RR 1.47, 95% CI 1.08 to 1.99) (AUST 2005; MELT 2007; PROACT 1 1998; PROACT 2 1999); trials where a majority of participants were treated with first-generation mechanical devices other than stent retrievers (e.g. Merci and Penumbra systems) (RR 1.05, 95% CI 0.87 to 1.27) (IMS III 2013; MR RESCUE 2013); and trials where a majority of participants were treated with stent retrievers (RR 1.80, 95% CI 1.59 to 2.04; P for interaction < 0.001) (Analysis 6.7) (BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; PISTE 2016; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015).

Proximity of vascular occlusion

There was a larger effect of the intervention in trials that included primarily proximal occlusion strokes, ESCAPE 2015; EXTEND-IA 2015; MR CLEAN 2015; REVASCAT 2015; SWIFT PRIME 2015, than in trials that included both proximal and non-proximal occlusion strokes, AUST 2005; IMS III 2013; MELT 2007; MR RESCUE 2013; PROACT 1 1998; PROACT 2 1999 (RR 1.71, 95% CI 1.47 to 1.99 versus RR 1.16, 95% CI 0.99 to 1.37; P for interaction < 0.001) (Analysis 6.8).

Infarct localisation

Some studies provided data on subgroups of stroke, but we were unable to compare these subgroups because of different definitions of stroke locations in each study (Analysis 6.9). Only one trial included participants with basilar artery occlusions (AUST 2005), but the sample size for this trial was too small for subgroup analyses.

Patient selection based on penumbra imaging

There was no difference in the effect of intervention between trials that used penumbra imaging for selection of patients to treatment (RR 2.24, 95% CI 1.45 to 3.46) DAWN 2018; DEFUSE 2018; EXTEND-IA 2015; MR RESCUE 2013; SWIFT PRIME 2015, and trials that did not use penumbra imaging (RR 1.72, 95% CI 1.42 to 2.08; P for interaction = 0.27) (Analysis 6.10) (AUST 2005; ESCAPE 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; PROACT 1 1998; PROACT 2 1999; REVASCAT 2015).

Sensitivity analyses

There was no difference in participants with good functional outcome between trials included the previous version of the review (AUST 2005; MELT 2007; PROACT 1 1998; PROACT 2 1999), compared with trials included in the current review (RR 1.47, 95% CI 1.08 to 1.99 versus RR 1.50, 95% CI 1.37 to 1.63; P for interaction = 0.91) (Analysis 7.1) (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; MR CLEAN 2015; MR RESCUE 2013; PISTE 2016; PROACT 1 1998; PROACT 2 1999; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016).

There was no difference in participants with good functional outcome between trials that included all planned participants (MR CLEAN 2015; MR RESCUE 2013; PROACT 2 1999), compared with trials that were stopped early (RR 1.55, 95% CI 1.22 to 1.98 versus RR 1.54, 95% CI 1.39 to 1.70; P for interaction = 0.95) (AUST 2005; BEST 2019; DAWN 2018; DEFUSE 2018; EASI 2017; ESCAPE 2015; EXTEND-IA 2015; IMS III 2013; MELT 2007; PISTE 2016; PROACT 1 1998; RESILIENT 2020; REVASCAT 2015; SWIFT PRIME 2015; THERAPY 2016; THRACE 2016).

The sensitivity analysis using a random-effects model (Analysis 7.3) found similar results compared to the fixed-effect model (Analysis 1.1). The RR was 1.54 (95% CI 1.33 to 1.78) in the random-effects model compared to RR 1.50 (95% CI 1.37 to 1.63) in the fixed-effect model.

DISCUSSION

Summary of main results

Since the first version of this review, we have added 15 new studies, bringing the total number of studies to 19, and the total number of participants up from 350 to 3793. With this substantial increase in evidence from randomised controlled trials, it has become clear that endovascular thrombectomy conveys important clinical benefits, with an increase in the chance of a good functional outcome (modified Rankin Scale score 0 to 2), and with no increase in the risk of symptomatic intracranial haemorrhage or death; there was in fact a reduction in the risk of death. The trials were generally of high methodological quality with low to unclear risk of bias, and the results were consistent with very little statistical heterogeneity, meaning that clinicians can be confident that the same results will apply in clinical practice, if similar patients are given similar treatment, in similar acute stroke services.

Subgroup analyses showed that the results apply irrespective of whether or not the participants had received intravenous thrombolytic therapy before the intervention, and irrespective of age and sex. Data were insufficient to determine the latest time for treatment to be effective, but subgroup analysis indicated that the results were better in participants with clinically more severe stroke, and in those with more pronounced early ischaemic changes on CT. Our subgroup analysis of four trials with 350 participants showed effect and benefit for functional outcome for intra-arterial thrombolysis, which adds important information to the ongoing discussion regarding treatment with intra-arterial thrombolysis for acute ischaemic stroke.

Overall completeness and applicability of evidence

The majority of participants in the included trials had anterior circulation infarcts caused by thrombotic occlusions in a proximal cerebral artery, as verified by CT or MRI angiography, and were treated within eight hours of symptom onset with the stent retriever technique. It is therefore uncertain whether the results can be extrapolated to individuals with posterior circulation infarcts, or to the use of other interventional techniques. Indeed, subgroup analysis showed a significantly lower effect amongst participants treated with techniques other than stent retrievers. We were not able to characterise the acute stroke services in which the participants were treated, so we cannot assess whether the results are limited to a certain organisation of services, or whether they apply irrespective of organisation.

Quality of the evidence

We prepared summary of findings tables using GRADE Pro GDT 2020 and Cochrane methods.

We are confident that the true effect lies close to that of the estimate of the effect.

The strengths of this review are that all of the included studies were either at a low or unclear risk of bias. A common source of heterogeneity in systematic reviews is differences in time of follow-up. All studies in our meta-analysis, with the exception of AUST 2005, measured outcome at 90 days' follow-up. This is therefore a strength of this review. As AUST 2005 included only 16 participants, we did not explore this in a subgroup analysis. Further, for all endovascular procedures there is a risk that no occlusions are identified for thrombectomy (Nogueira 2013). This may attenuate the results and may introduce bias.

The weaknesses of this review are that some studies were small, and studies included different types of endovascular treatments, such as either endovascular thrombectomy or intra-arterial interventions, or a combination of the two. Furthermore, only one trial was double-blinded (PROACT 1 1998). This trial was of intra-arterial thrombolysis and did not include mechanical thrombectomy. It is not possible to blind the interventionist when performing mechanical endovascular thrombectomy. Another weakness is that 16 trials were terminated prematurely and therefore lacked statistical power.

Potential biases in the review process

We minimised potential biases in the review process 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 risk of bias assessment.

Agreements and disagreements with other studies or reviews

Our review is in line with two recently published systematic reviews of endovascular thrombectomy for acute ischaemic stroke, which showed positive effect of endovascular thrombectomy for acute ischaemic stroke (Lin 2019; Zhao 2020). With its thorough search strategies and identification of more studies than these two meta-analyses, our review adds to the literature.

AUTHORS' CONCLUSIONS

Implications for practice

We found high-certainty evidence that endovascular thrombectomy improves functional and neurological outcomes without increasing haemorrhage or death. The benefit was seen with/without intravenous thrombolysis and was unrelated to age, sex, and time to intervention (although most participants were treated within six hours of symptom onset). Benefits were greater with more severe stroke.

Implications for research

Very few trials included individuals with posterior circulation infarcts, but trials are underway that will try to answer whether similar benefits can be achieved in such patients (NCT01717755). New trials are also needed to confirm the maximum time window for endovascular thrombectomy to be effective, and how advanced imaging techniques should be used to identify patients who might benefit from treatment in the late hours after stroke onset. We also expect that with time and research development of endovascular thrombectomy, new techniques will emerge.

On a population level, there is a need to investigate whether a strategy of primary endovascular thrombectomy is superior to a strategy with primary intravenous thrombolytic treatment in a local centre followed by transfer of eligible patients to an interventional centre. If such a strategy is superior, what is the maximum time delay for primary endovascular thrombectomy intervention to be superior to intravenous thrombolysis followed by intervention?

Furthermore, endovascular thrombectomy is performed by professionals from many disciplines, including neuroradiologists, general interventional radiologists, neurologists, neurosurgeons, and cardiologists. It is unknown whether the effect of treatment depends on the professional background of the interventionalist or the annual number of procedures. This information is important for determining whether endovascular thrombectomy could be provided by interventional cardiologists or radiologists in smaller hospitals.

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CHARACTERISTICS OF STUDIES

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

AUST 2005

Study characteristics	
Methods	RCT
Participants	Patients with acute posterior circulation stroke, confirmed by digital subtraction angiography Glasgow Coma Scale score ≥ 9 Age 18 to 85 years
Interventions	Endovascular intra-arterial intervention (IA thrombolysis with UK) plus anticoagulation versus anticoagulation alone, within 24 hours of stroke onset. UK was given in increments of 100,000 IU to a maximum of 1,000,000 IU. All participants received intra-arterial heparin as a 5000-international unit bolus followed by infusion to maintain an APTT of 60 to 80 seconds for a minimum of 2 days, and then oral warfarin to maintain an INR of 1.5 to 2.5 for 6 months.
Outcomes	Primary outcome: death or disability (Barthel Index and modified Rankin Scale scores) at 6 months Secondary outcomes: • degree of recanalisation at 7 to 10 days; • neurological impairment at 6 months; • safety and tolerability of intra-arterial UK; • cost-effectiveness of therapy.
Funding source	Unrestricted educational grant from Serono and by an intramural grant from the National Health and Medical Research Council of Australia

AUST 2005 *(Continued)*

Notes	There was no clear definition of sICH.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation by telephone with a central office, and subsequently by the pharmacy department at the Royal Melbourne Hospital. In 2 cases participants were randomised by coin toss in the treating centre, a practice approved by the trial steering committee. Concealment of allocation was considered to be adequate in each case, but a lack of detail with regard to the randomisation methodology used by the trial sponsor and Royal Melbourne Hospital pharmacy department means that it remains unclear whether sequence generation was satisfactory.
Allocation concealment (selection bias)	Unclear risk	Randomisation by telephone with a central office, and subsequently by the pharmacy department at the Royal Melbourne Hospital. In 2 cases participants were randomised by coin toss in the treating centre, a practice approved by the trial steering committee. Concealment of allocated treatment was considered to be adequate in each case, but a lack of detail with regard to the randomisation methodology used by the trial sponsor and Royal Melbourne Hospital pharmacy department means that it remains unclear whether sequence generation was satisfactory.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). All outcomes were determined by an independent outcomes committee who were blinded to treatment allocation. Clinical outcomes were determined at 6 months by a certified research nurse or a neurologist blinded to treatment allocation and who was not involved in the participant's initial care.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to clinical follow-up
Selective reporting (reporting bias)	High risk	Secondary outcomes not reported. Baseline angiographic findings not reported for 2 participants. No a priori requirement for follow-up imaging
Other bias	Unclear risk	The trial was stopped early because of slow recruitment and the withdrawal from sale of urokinase.

BEST 2019

Study characteristics

Methods	Randomised controlled, multicentre, open-label trial at 28 centres in China
Participants	Patients presenting within 8 hours of vertebrobasilar occlusion
Interventions	Endovascular therapy plus standard medical treatment or standard medical therapy alone. The endovascular procedure consisted of mechanical thrombectomy with stent retriever (the preferred method) or thrombo-aspiration devices.
Outcomes	Primary outcome: modified Rankin Scale score of 3 or lower at 90 days assessed on an intention-to-treat basis

BEST 2019 *(Continued)*

Funding source	Jiangsu Provincial Special Program of Medical Science
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation and stratified by participating centres
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias)Assessment was done by certified rater not aware of the trial group assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up. Reported all participants and intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Unclear risk	The trial was terminated prematurely by the steering committee based on recommendations from the data and safety monitoring board regarding excessive cross-overs and progressive drop in the average rate of valid per-centre recruitment.

DAWN 2018

Study characteristics

Methods	Randomised, multicentre, open-label, controlled phase II/III, treatment trial
Participants	Clinical signs and symptoms consistent with the diagnosis of an acute ischaemic stroke, and participant belongs to one of the following subgroups: (1) participant has failed IV-tPA therapy (defined as a confirmed persistent occlusion 60 minutes after administration), (2) participant is contraindicated for IV-tPA administration Age ≥ 18 years Baseline NIHSS ≥ 10 (assessed within 1 hour prior to measuring core infarct volume) Participant may be randomised between 6 to 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	Endovascular thrombectomy treatment (Trevo stent) plus best medical management vs best medical management. Thrombectomy was performed with the use of the Trevo device, a retrievable stent. Rescue reperfusion therapy or pharmacological agents were not permitted.
Outcomes	Weighted modified Rankin Scale score at 90 days follow-up
Funding source	Stryker Neurovascular
Notes	Terminated early due to efficacy

DAWN 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed with a central web-based procedure with block minimisation to balance the 2 groups and stratified according to mismatch criteria.
Allocation concealment (selection bias)	Low risk	Quote from protocol: "If the subject's eligibility status is confirmed, the server allocates the treatment"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias)Outcome assessment was performed by certified assessors unaware of treatment assignment. Adjudication performed by an independent clinical-events committee.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up. Reported all participants and intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Low risk	At 31 months and 206 participants enrolled, the trial was stopped prematurely because of the results of a prespecified interim analysis.

DEFUSE 2018

Study characteristics	
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 internal carotid artery 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 therapy (thrombectomy) plus standard medical treatment vs standard medical treatment alone. Thrombectomy was performed with any Food and Drug Administration-approved thrombectomy device at the discretion of the neurointerventionalist. Intra-arterial tissue plasminogen activator was not allowed.
Outcomes	Primary outcome: ordinal core on the modified Rankin Scale at 90 days follow-up
Funding source	National Institute of Neurological Disorders and Stroke
Notes	

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

DEFUSE 2018 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote from protocol: "When a new patient is enrolled, the site enters the stratification factor values into the electronic case report form (eCRF) on WebDCU. The dynamic randomization algorithm determines an imbalance measure for each treatment group". Allocation is done by the server after enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Outcome assessed by certified rater who was blinded to trial assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants lost to follow-up and intention-to-treat analysis provided.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Low risk	After an early interim analysis following the DAWN trial results and at 182 randomised participants, the trial was halted due to efficacy.

EASI 2017

Study characteristics	
Methods	Randomised, open-label, controlled phase III, treatment trial
Participants	Age ≥ 18 years NIHSS ≥ 8 Onset of symptoms is less than 5 hours or symptom/imaging mismatch Suspected occlusion of the M1 or M2 segment of the MCA, supraclinoid internal carotid artery, or basilar trunk
Interventions	Standard care plus mechanical thrombectomy versus standard care alone. Thrombectomy was performed under local or general anaesthesia using any approved device according to local practice.
Outcomes	Favourable functional outcome, defined as modified Rankin Scale score 0 to 2 at 90 days follow-up
Funding source	No funding source for this study
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-based. Minimisation procedure was used as a method of adaptive stratified sampling.
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). All data and outcome measures were collected by unblinded routine care personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up and intention-to-treat analysis provided.

EASI 2017 *(Continued)*

Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Unclear risk	Randomised allocation stopped November 2014 when benefit was shown by other trials. 10 participants randomised to interventional management did not receive this. 3 participants were cross-overs from standard treatment to intervention.

ESCAPE 2015

Study characteristics	
Methods	RCT
Participants	Patients with a proximal intracranial occlusion in the anterior circulation were included up to 12 hours after symptom onset. Patients with a large infarct core or poor collateral circulation on CT and CT angiography were excluded.
Interventions	Standard care according to local guidelines (control group) Standard care plus endovascular thrombectomy intervention with the use of available thrombectomy devices (intervention group). The neurointerventionalist used available thrombectomy devices to achieve reperfusion. The use of retrievable stents was recommended. Suction through a balloon guide catheter in the relevant internal carotid artery during thrombus retrieval was recommended.
Outcomes	Primary outcome was modified Rankin Scale score at 90 days. Secondary outcomes were NIHSS score 0 to 2 at 90 days follow-up, Barthel Index score 95 to 100 at 90 days follow-up, TICI score 2b/3 at final angiogram in the intervention group. EuroQoL 5-Dimension (EQ-5D) self-report questionnaire at 90 days follow-up. Serious adverse events were death at 90 days follow-up, large or malignant MCA stroke, sICH, haemorrhage at access site, and perforation of the MCA.
Funding source	Funded by Cividien and others
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Real-time, dynamic, internet-based, randomisation with minimisation procedure to achieve distribution balance with regard to age, sex, baseline NIHSS score (range 0 to 42), site of arterial occlusion, baseline ASPECT score, and status with respect to intravenous alteplase treatment
Allocation concealment (selection bias)	Low risk	Quote from protocol: "Because randomisation will occure dynamically in real-time, it will be fully concealed"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Clinical outcomes were assessed by trained personnel blinded to treatment allocation. Interpretation of images was performed at an external core laboratory by personnel blinded to treatment allocation.

ESCAPE 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants (1.3%) were lost to follow-up. Missing outcome data for these participants were not imputed.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses
Other bias	Unclear risk	The trial was stopped early because of evidence of efficacy after an interim analysis following the MR CLEAN results and at 316 randomised participants.

EXTEND-IA 2015

Study characteristics	
Methods	RCT
Participants	Patients were eligible if they could receive intravenous alteplase within 4.5 hours after the onset of anterior circulation ischaemic stroke and had occlusion of the internal carotid artery or of the first or second segment of the MCA, as seen on CT angiography. Patients were eligible if CT perfusion imaging showed salvageable brain tissue and ischaemic core of < 70 mL. Intervention had to be initiated (groin puncture) within 6 hours after stroke onset and completed within 8 hours after onset. There were no restrictions on age or clinical severity according to NIHSS score. Participants were required to have functional independence before the stroke episode, defined as mRS score 0 to 2.
Interventions	Thrombectomy with the Solitaire FR (Flow Restoration) stent retriever (intervention group) No intra-arterial treatment (controls) All participants received 0.9 mg of alteplase per kilogram of body weight less than 4.5 hours after the onset of ischaemic stroke.
Outcomes	Primary outcomes: • reperfusion at 24 hours; and • early neurological improvement (defined as reduction of NIHSS score ≥ 8 or score 0 to 1 at day 3). Secondary outcomes: death, mRS score at 90 days follow-up, and sICH
Funding source	Australian National Health and Medical Research Council and others
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation procedure was computer-generated randomisation code lists, with stratification for site of baseline arterial occlusion.
Allocation concealment (selection bias)	Low risk	Quote from protocol: "once patient recruitment data are submitted by the site staff via EXTEND-IA online, the randomization iss immediately provided back to the investigator."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Radiological outcome measures were centrally analysed, blinded to assigned treatment. Neurological impair-

EXTEND-IA 2015 *(Continued)*

		ment and functional scores were measured by a clinician blinded to assigned intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up and intention-to-treat analysis provided.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Unclear risk	The trial was stopped early because of evidence of efficacy after 70 participants had undergone randomisation and because of the publication of MR CLEAN.

IMS III 2013

Study characteristics	
Methods	RCT
Participants	Patients who had received intravenous r-tPA within 3 hours after symptom onset. In the first part of the study, patients were eligible if they had an NIHSS score of 10 or higher. After 284 of the 656 participants were included, identification of occlusion with the use of CT angiography was allowed to determine trial eligibility for patients with an NIHSS score of 8 or 9.
Interventions	All participants received intravenous r-tPA (0.9 mg/kg), with 10% as a bolus and the remainder infused over a 1-hour period (maximum dose 90 mg). Randomisation was required within 40 minutes after the initiation of the infusion. Participants randomly assigned to IV r-tPA received the remainder of the standard dose. In the first part of the trial, participants randomised to the endovascular thrombectomy intervention only received 2/3 of the standard IV dose, plus any r-tPA given intra-arterially. During the latter part of the trial, participants randomised to the endovascular intervention received the full standard IV dose. The angiographic procedure had to begin within 5 hours and be completed within 7 hours after the onset of stroke. Heparin infusion was started intravenously with a 2000-unit bolus, followed by an infusion of 450 units per hour during endovascular therapy, and was discontinued at the end of the procedure. The method of endovascular intervention was determined by the neurointerventionalist, who could choose between mechanical thrombectomy with stent retrievers, Penumbra system or Solitaire FR revascularisation device or endovascular intra-arterial delivery of tPA by means of microcatheter.
Outcomes	modified Rankin Scale score of 2 or less at 90 days
Funding source	National Institutes of Health and others
Notes	The planned sample size was 900 participants.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-based randomisation using a computer-based algorithm.
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelope".

IMS III 2013 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Outcome assessment was by personnel blinded to allocated treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	An unfavourable imputation was applied for 27 participants (14 participants for whom the primary outcome was assessed outside the specified 30-day window, and 13 for whom the primary outcome was not assessed).Intention-to-treat analysis was provided.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Unclear risk	The study was stopped early because of futility after 656 participants had undergone randomisation following a prespecified rule. A total of 23% participants randomised to intervention did not receive thrombectomy because there was no lesion identified during the endovascular procedure.

MELT 2007

Study characteristics	
Methods	RCT
Participants	Acute MCA territory ischaemic stroke allowing initiation of treatment within 6 hours of stroke onset Participants were randomised when digital subtraction angiography of the symptomatic carotid artery territory showed complete occlusion of either the horizontal M1 or the M2 division of the MCA. NIHSS at least 5 Age 20 to 75 years
Interventions	Intra-arterial thrombolysis with urokinase ± mechanical clot disruption with guidewire vs no such treatment, against a background of standard medical care not including IV-tPA. 5000 IU heparin were infused prior to introducing the angiogram sheath. The microcatheter was passed through the clot, and urokinase was infused beyond the distal margin of the thrombus as repeated boluses of 120,000 IU over 5 minutes to a maximum of 600,000 IU, which were discontinued if complete recanalisation was achieved. Antithrombotic therapies including heparin, warfarin, and aspirin were prohibited for 24 hours after thrombolysis in the treatment group.
Outcomes	Primary outcome: favourable clinical outcome, defined as mRS score of 0 to 2 at 3 months Secondary outcomes: • sICH within 24 hours of starting treatment; • degree of recanalisation; • NIHSS score 0 to 1 at 24 hours, 30 days, 90 days; • Barthel Index score at least 95 at 30 days, 90 days; • mRS score 0 to 1 at 30 days, 90 days; • any haemorrhagic finding on CT.
Funding source	Grants-in-Aid from the Ministry of Health, Labor and Welfare of Japan
Notes	In this study sICH was defined as CT evidence of apparent neurological deterioration manifesting as either "objective signs" or an increase of at least 4 points from the most recent NIHSS score. As has been previously pointed out (Saver 2007), the process for adjudicating new "objective signs" is not well delineated and confounds direct comparison with National Institute of Neurologic Diseases and Stroke-defined sICH rates.

MELT 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation by a central randomisation centre via the internet, but the precise methodology used for randomisation was not explained, therefore it remains unclear whether sequence generation was adequate.
Allocation concealment (selection bias)	Low risk	Central randomisation via internet
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). All angiograms were evaluated by the film reading committee, who were unaware of the clinical information. Clinical outcome was assessed by physicians unaware of the treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat results presented. 1 participant was not randomised due to computer error. No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Unclear risk	The trial was stopped early by the steering committee following a recommendation by the independent monitoring committee when IV-tPA became available in Japan. The recommendation was that the trial be either modified so as not to include patients presenting within 3 hours of stroke onset, or terminated. We did not consider this to be a potential source of bias. No information provided regarding conventional vascular risk factors possibly related to outcome.

MR CLEAN 2015

Study characteristics

Methods	RCT
Participants	A clinical diagnosis of acute stroke, with a deficit on the NIHSS of 2 points or more CT or MRI scan ruling out intracranial haemorrhage Intracranial arterial occlusion of the distal intracranial carotid artery or middle (M1/M2) or anterior (A1/A2) cerebral artery, demonstrated with CT angiography, magnetic resonance angiography, digital subtraction angiography, or transcranial Doppler/duplex The possibility to start treatment within 6 hours from onset Informed consent given Age 18 years or over
Interventions	Approved intervention was both intra-arterial treatment, which consisted of arterial catheterisation with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, or mechanical thrombectomy, or both. The method of endovascular intervention was left to the discretion of the local neurointerventionist. The use of alteplase and UK for intra-arterial thrombolysis was allowed in this trial with a maximum dose of 90 mg of alteplase and 1,200,000 IU of UK. Mechanical treatment could involve thrombus retraction, aspiration, wire disruption, or use of a retrievable stent. Endovascular intervention plus best medical therapy vs best medical therapy alone

MR CLEAN 2015 *(Continued)*

Outcomes	Score on the modified Rankin Scale at 3 months
Funding source	Dutch Heart Foundation and others
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer- and web-based randomisation with the use of permuted blocks. Stratified according to medical centre, use of intravenous alteplase, planned treatment method, and stroke severity
Allocation concealment (selection bias)	Low risk	Randomisation done centrally over Internet or telephone after patient has been included.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Blinded outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants lost to follow-up (withdrew consent after randomisation), and intention-to-treat analysis provided
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses
Other bias	Low risk	Not terminated prematurely

MR RESCUE 2013

Study characteristics

Methods	RCT
Participants	New focal disabling neurologic deficit consistent with acute cerebral ischaemia (NIHSS ≥ 6) Age ≥ 18 ≤ 85 years Clot retrieval procedure can be initiated within 8 hours from onset Large vessel proximal anterior circulation occlusion on magnetic resonance imaging or CT angiography (internal carotid, M1 or M2 MCA) Pretreatment MRI performed according to MR RESCUE protocol Signed informed consent obtained from the patient or patient's legally authorised representative Premorbid modified Rankin Scale score of 0 to 2 Allowed but not required: patients treated with IV-tPA up to 4.5 hours from symptom onset with persistent target occlusion on post-treatment MR RESCUE MR or CT protocol performed at the completion of drug infusion (Note: rapidly improving neurological signs prior to randomisation is an exclusion)
Interventions	Mechanical thrombectomy (Merci Retriever or Penumbra System) plus best medical treatment vs best medical treatment. Participants in the embolectomy group could be treated with any combination of FDA-cleared embolectomy devices, including the Merci Retriever and the Penumbra System. Intra-arterial administration of tPA at a dose of as much as 14 mg was allowed as rescue therapy within 6 hours after symptom onset.
Outcomes	modified Rankin Scale score 0 to 2 at 90 days follow-up

MR RESCUE 2013 *(Continued)*

Funding source	National Institute of Neurological Disorders and Stroke
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation. Stratified according to penumbral pattern on brain imaging
Allocation concealment (selection bias)	Low risk	Central allocation through telephone after enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol analyses. 9 participants excluded from the analyses (5 did not have target lesion on vessel imaging; 2 did not have post-tPA vessel imaging; 2 had failed perfusion imaging).
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses
Other bias	Low risk	Not terminated prematurely

PISTE 2016

Study characteristics

Methods	Randomised controlled, multicentre, open-label, phase III treatment trial
Participants	Patients aged 18 years and older Clinically significant neurological deficit and NIHSS score ≥ 6 Enrolment, randomisation, and procedure commencement (groin puncture) possible within 90 minutes of the start of IV r-tPA treatment (groin puncture maximum 5.5 hours after stroke onset) Occlusion of the main MCA trunk, MCA bifurcation or intracranial internal carotid artery (carotid T, M1 or single proximal M2 branch) demonstrated on Computed Tomography Angiogram, Magnetic Resonance Angiogram or Digital Subtraction Angiography
Interventions	Mechanical thrombectomy vs best medical management. Both groups were given intravenous thrombolytic treatment.
Outcomes	modified Rankin Scale score 0 to 2 at 90 days follow-up
Funding source	Stroke Association, National Institute of Health Research Health Technology Assessment Programme, unrestricted grants from Codman and Covidien and others
Notes	Trial stopped early because of results from other trials.

Risk of bias

Bias	Authors' judgement	Support for judgement

PISTE 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-based randomisation with a minimisation algorithm for age, stroke severity, and symptom-onset to treatment time
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up. Intention-to-treat analysis provided.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses
Other bias	Low risk	Trial terminated early after review of other trial data.

PROACT 1 1998

Study characteristics	
Methods	RCT (phase II)
Participants	Acute MCA territory ischaemic stroke allowing initiation of treatment within 6 hours of stroke onset. Cerebral angiography of the symptomatic carotid artery territory had to show complete occlusion (TIMI grade 0) or contrast penetration with minimal perfusion (TIMI grade 1) of either the horizontal M1 or the M2 division of the middle cerebral artery. NIHSS 4 to 30, but patients with isolated aphasia or hemianopia were also included Age 18 to 85 years
Interventions	Intra-arterial thrombolysis with pro-UK versus no such treatment against a background of standard medical care not including IV-tPA. All participants received IV heparin for 4 hours after angiographic demonstration of an occluding thrombus. The rate of infusion varied throughout the trial as follows: the first 16 patients received a 100 IU/kg bolus followed by 1000 IU/hour infusion. On the recommendation of the external safety committee, the regimen was altered to a 2000-international unit bolus followed by 500 IU/hour infusion. Oral anticoagulants were prohibited for 24 hours following treatment. The PROACT method was to position the microcatheter in the proximal third of the target clot and thereby to infuse rpro-UK directly into the thrombus over a period of 120 minutes; the entire dose was given irrespective of any recanalisation achieved within the 120-minute infusion period. The dose of rpro-UK was 6 mg.
Outcomes	Primary efficacy outcome: recanalisation of M1 or M2 MCA at 120 minutes after initiation of treatment Primary safety outcome: sICH within 24 hours of treatment. Clinical outcome was assessed at 7, 30, and 90 days post-treatment (on-treatment analysis).
Funding source	Abbott Laboratories (Abbott Park, Ill) is the sponsor of the trial
Notes	The protocol for follow-up imaging in this study and PROACT 2 1999 is unclear.
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

PROACT 1 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Central randomisation centre assigned participants to the treatment or control groups, which we considered to be adequate concealment of allocation. However, the precise randomisation methodology was not explained, therefore it remains unclear whether sequence generation was adequate.
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind trial: control participants received IA saline placebo. All investigators and examining physicians were blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	No participants lost to follow-up. This study did not report the primary efficacy outcome for 6 randomised but untreated participants (i.e. an on-treatment rather than the preferred intention-to-treat analysis). 5 of these 6 participants were in the treatment group, representing 16% of the total randomised treatment group; the remaining randomised but untreated participant was in the placebo group. Given the possibility that the 5 participants randomised to the treatment group who did not receive treatment represent a subgroup of non-responders, this may have had the effect of enriching the treatment group with responders and biasing the results in favour of treatment. The primary safety outcome was reported for these 6 participants, therefore we do not consider that the safety analysis was prone to on-treatment bias. Any on-treatment bias due to these 6 participants would be diluted in the overall analysis.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.
Other bias	Unclear risk	No information provided regarding conventional vascular risk factors possibly related to outcome Trial stopped early by sponsor to determine whether there was sufficient evidence of safety and efficacy to support continuation of a longer-term programme, ultimately expressed in the form of the phase III PROACT 2 1999 trial. No safety concerns were involved in that decision. An analysis of the data set from all patients who underwent angiography by a biostatistical unit independent of the conduct of the trial forms the basis of the published PROACT 1 1998 report. At the time of termination, the PROACT 1 1998 trial had achieved 89% of its target sample size. The implications are difficult to interpret. As a general principle, trials that are stopped for any reason other than according to specific predefined stopping rules are theoretically prone to bias. However, it remains unclear whether this factor introduced any bias in this particular case.

PROACT 2 1999

Study characteristics	
Methods	RCT (phase III)
Participants	Acute MCA territory ischaemic stroke allowing initiation of treatment within 6 hours of stroke onset. TIMI grade 0 or 1 in either M1 or M2. NIHSS 4 to 30, or isolated aphasia or hemianopia Age 18 to 85 years
Interventions	Intra-arterial intervention with pro-urokinase versus no such treatment against a background of standard medical care not including IV-tPA. See PROACT 1 1998 for more details.
Outcomes	Primary outcome: favourable clinical outcome, defined as an mRS score of 0 to 2 at 3 months

PROACT 2 1999 *(Continued)*

	Secondary outcomes: • NIHSS 0 to 1 at 90 days; • rate of angiographic recanalisation; • at least 50% reduction in baseline NIHSS at 90 days; • Barthel Index scores of at least 60 at 90 days. Clinical outcomes were assessed in a standardised fashion at 7, 10, 30, and 90 days following randomisation by the same board-certified or "eligible" neurologist in each centre. All examiners were required to pass certifying examinations for the NIHSS and Barthel Index, with a requirement for NIHSS re-certification after approximately 6 months.
Funding source	Abbott Laboratories
Notes	Published analyses performed independently of the sponsor.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated master randomisation schedule using a random block size was used for sequence generation.
Allocation concealment (selection bias)	Low risk	A blinded randomisation code was assigned by telephone independent of the sponsor. The schedule was not stratified by clinical centre to preclude knowledge of the distribution of future treatment assignments at a given centre.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). All CT and 2-hour angiograms were assessed by a neuroradiologist at a core facility who was blinded to treatment assignment and clinical status. Follow-up examinations were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat results reported. Some participants carried forward. Some appropriate imputation used. No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.
Other bias	High risk	Significant excess of diabetics in control group. This is a potential source of bias.

RESILIENT 2020

Study characteristics

Methods	Randomised controlled, multicentre, open-label, prospective, blinded outcome evaluation trial
Participants	Patients with proximal arterial occlusion in the anterior circulation that could be treated within 8 hours after onset of stroke symptoms
Interventions	Standard care plus mechanical thrombectomy or standard care alone. In the intervention group, thrombectomy was performed with the Solitaire FR stent retriever or Penumbra aspiration system. Standard medical care including the use of intravenous alteplase followed national and AHA medical guidelines.

RESILIENT 2020 *(Continued)*

Outcomes	Primary outcome: disability at 90 days evaluated by the distribution of scores on the modified Rankin Scale
Funding source	Unrestricted grant from the Brazilian Ministry of Health
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed in real time by dynamic, internet-based procedure and with a minimisation algorithm.
Allocation concealment (selection bias)	Low risk	Central randomisation after patient had been recruited into the trial.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses were conducted according to the intention-to-treat principle. 1 participant lost to follow-up
Selective reporting (reporting bias)	Low risk	Reported prespecified outcomes
Other bias	Low risk	Trial was terminated early because of efficacy.

REVASCAT 2015

Study characteristics

Methods	RCT
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 recanalisation after a minimum of 30 minutes from start of IV-tPA infusion No significant pre-stroke functional disability (mRS ≤ 1) Baseline NIHSS score obtained prior to randomisation must be equal or higher than 6 points Age ≥ 18 and ≤ 85 years Occlusion (TICI 0 to 1) of the intracranial internal carotid artery (distal ICA or T occlusions), MCA-M1 segment or tandem proximal ICA/MCA-M1 suitable for endovascular treatment, as evidenced by computed tomography angiogram, magnetic resonance angiogram or angiogram, with or without concomitant cervical carotid occlusion or stenosis Hypodensity on CT or restricted diffusion amounting to an ASPECTS of < 7 on non-contrast CT or < 6 on DWI MRI. Patients 81 to 85 years old with ASPECTS on non-contrast CT or DWI MRI < 9 were excluded. ASPECTS must be evaluated by cerebral blood volume maps of CT perfusion, CTA source imaging (CTA-SI), or DWI-MR in patients whose vascular occlusion study (CTA/MRA) confirming qualifying occlusion is performed beyond 4.5 hours of last seen well.
Interventions	Endovascular thrombectomy with the Solitaire stent retriever and medical therapy (including intravenous alteplase when eligible) versus medical treatment alone. Study sites had to perform more than

REVASCAT 2015 *(Continued)*

	60 mechanical thrombectomy procedures annually to be eligible, and the neurointerventionalists must have performed more than 20 thrombectomies with the Solitaire device.
Outcomes	modified Rankin Scale score 0 to 2 at 90 days follow-up
Funding source	Fundació Ictus Malaltia Vascular through an unrestricted grant from Covidien and others
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Real-time computerised randomisation stratified according to age, baseline NIHSS, therapeutic window, occlusion site, and participating centre
Allocation concealment (selection bias)	Low risk	Real-time, central computerised randomisation stratified according to age, baseline NIHSS, therapeutic window, occlusion site, and participating centre. Done after recruitment to trial.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant lost to follow-up (withdrew consent)
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses
Other bias	Low risk	Trial was terminated early because of lack of equipoise after positive results from other similar trials at 206 randomised participants.

SWIFT PRIME 2015

Study characteristics

Methods	RCT
Participants	Age 18 to 80 years Clinical signs consistent with acute ischaemic stroke NIHSS scores ≥ 8 and < 30 at the time of randomisation Initiation of IV-tPA within 4.5 hours of onset of stroke symptoms (onset time is defined as the last time when the patient was witnessed to be at baseline), with investigator verification that the patient has received/is receiving the correct IV-tPA dose for the estimated weight prior to randomisation TICI 0 to 1 flow in the intracranial internal carotid artery, M1 segment of the MCA, or carotid terminus confirmed by CT or MR angiography that is accessible to the Solitaire FR Device Patient can be treated within 6 hours of onset of stroke symptoms and within 1.5 hours (90 minutes) from CTA or MRA to groin puncture Baseline non-contrast CT or DWI MRI evidence of a small core defined as early ischaemic changes of ASPECTS ≥ 6 Anterior circulation stroke on CTA or MRA

SWIFT PRIME 2015 *(Continued)*

Interventions	Intravenous alteplase followed by endovascular thrombectomy with the use of Solitaire FR or Solitaire 2 device versus intravenous alteplase and best medical treatment alone
Outcomes	modified Rankin Scale score 0 to 2 at 90 days follow-up
Funding source	Covidien
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a minimisation algorithm for investigational site, stroke severity, age, and occlusion location
Allocation concealment (selection bias)	Low risk	Quote from protocol: "At the time of randomization, the site will access IVRS and enter subject's NHSS, age and occlusion location. Based on the information provided, the system will automatically generate the assigned treatment".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses
Other bias	Low risk	Trial was terminated early because of efficacy after 196 participants.

THERAPY 2016

Study characteristics	
Methods	Randomised, multicentre, open-label, controlled phase III, treatment trial
Participants	Age 18 to 85 years Presenting symptoms consistent with an acute ischaemic stroke and eligible for IV r-tPA therapy (patients presenting 3 to 4.5 hours from symptom onset are not eligible if they are > 80 years of age, have a history of stroke and diabetes, anticoagulant use (even if INR is < 1.7), and have an NIHSS score > 25) Evidence of a large vessel occlusion in the anterior circulation with a clot length of 8 mm or longer NIHSS score 8 or greater or aphasic at presentation Signed informed consent
Interventions	Intravenous alteplase alone versus thrombectomy using mainly the Penumbra System and intravenous alteplase. In the intervention group, traditional separator-based aspiration system (Penumbra) was used in 30 participants (54%), the Separator 3D in 14 participants (25%), the ACE catheter (Penumbra) in 15 participants (27%), and either a Solitaire Covidien or Trevo Stryker in 7 participants (13%).
Outcomes	modified Rankin Scale score 0 to 2 at 90 days follow-up

THERAPY 2016 *(Continued)*

Funding source	No specific grant from funding agencies in the public, commercial, or not-for-profit sectors
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Performed by centralised interactive voice response system. Stratified according to enrolling centre
Allocation concealment (selection bias)	Low risk	Performed by centralised interactive voice response system. Stratified according to enrolling centre
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Outcome assessment was performed by blinded, trained, certified investigators and assessed by independent blinded adjudicators.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12 participants were lost to follow-up. Intention-to-treat analysis provided.
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Low risk	Trial enrolment was halted by steering committee after results from MR CLEAN.

THRACE 2016

Study characteristics	
Methods	Randomised multicentre clinical trial
Participants	Acute ischaemic stroke, NIHSS 11 to 24 Onset to randomisation within 3 hours Occlusion of the intracranial carotid, the MCA (M1) or the upper third of the basilar artery
Interventions	Standard intravenous thrombolysis with alteplase followed by mechanical thrombectomy in the treatment group versus standard intravenous thrombolysis with alteplase alone in the control group. In the treatment group, a complementary intra-arterial injection of a maximum of 0.3 mg/kg of alteplase at the end of thrombectomy was authorised only in cases of persistent distal occlusions. The neurointerventionalist had to choose a device from the trial's regularly updated list of thrombectomy devices and had to show proof of performance of at least 5 procedures with the chosen device before using it in the trial.
Outcomes	Primary outcome: modified Rankin Scale score at 90 days Secondary outcomes: quality of life (EuroQoL 5-Dimension (EQ-5D)) at 90 days, Barthel Index score at 90 days
Funding source	French Ministry of Health
Notes	Trial was terminated due to efficacy.

THRACE 2016 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by computer analyst masked to centre and participants with the help of a computer-generated sequence and stratified by centre and sequential minimisation to avoid imbalance.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was done at the coordination centre by a computer analyst who was masked to the investigation centres and to the patients".
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding of participants and personnel in regards to treatment allocation in this trial, (performance bias). Experienced independent interventional neuroradiologists who were masked to participant clinical outcome and other imaging assessed the angiograms before and after thrombectomy. Clinical assessments were made by vascular neurologists not masked to the treatment allocated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 participants lost to follow-up and with missing data were excluded from analysis (modified intention-to-treat analysis).
Selective reporting (reporting bias)	Low risk	Reported prespecified analyses.
Other bias	Low risk	Trial Steering Committee terminated trial early after 414 participants because of efficacy.

AHA: American Heart Association
APTT: activated partial thromboplastin time
ASPECTS: Alberta Stroke Program Early CT Score
CT: computed tomography
IA: intra-arterial
INR: international normalised ratio
IU: international units
IV-tPA: intravenous tissue plasminogen activator
MCA: middle cerebral artery
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
RCT: randomised controlled trial
rpro-UK: recombinant pro-urokinase
r-tPA: recombinant tissue plasminogen activator
sICH: symptomatic intracerebral haemorrhage
TICI: thrombolysis in cerebral infarction
TIMI: thrombolysis in myocardial infarction
tPA: tissue plasminogen activator
UK: urokinase

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

Study	Reason for exclusion
Ducrocq 2005	This is not a comparison of IA-tPA versus control, since only the control group is given IV-tPA.

Study	Reason for exclusion
Keris 2001	This is not a comparison of IA-tPA versus control, since the intervention group received both IV-tPA and IA-tPA.
Lewandowski 1999	This is not a comparison of IA-tPA versus control (no IA-tPA), since both groups received IA-tPA. The control group was given IA-tPA, which is not the protocol definition of 'routine medical treatment'.
Sen 2009	This is not a comparison of IA-tPA versus control, since only the control group is given IV-tPA.
SYNTHESIS Expansion 2013	This is not a comparison of IA-tPA versus control, since only the control group is given IV-tPA.
SYNTHESIS pilot 2010	This is not a comparison of IA-tPA versus control, since only the control group is given IV-tPA.
Wolfe 2008	This is not a comparison of IA-tPA versus control (no IA-tPA), since both groups received IA-tPA. The control group was given IA-tPA, which is not the protocol definition of 'routine medical treatment'.

IA-tPA: intra-arterial tissue plasminogen activator
IV-tPA: intravenous tissue plasminogen activator

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

ISRCTN19922220

Study name	Endovascular treatment of acute stroke for late arrivals
Methods	Multicentre, randomised treatment allocation, open-label treatment and blinded endpoint evaluation
Participants	Patients with acute ischaemic stroke, intracerebral haemorrhage ruled out with non-contrast CT, a confirmed intracranial anterior circulation occlusion and poor-to-good collaterals on CTA will be included. Treatment should be started between 6 and 24 hours after symptom onset. Age should be 18 or over and NIHSS 2 or more.
Interventions	Endovascular treatment versus no endovascular treatment. The treatment is provided in addition to best medical management.
Outcomes	The primary outcome is the score on the modified Rankin Scale at 90 days after inclusion.
Starting date	December 2017
Contact information	late.trialoffice@mumc.nl
Notes	

NCT01717755

Study name	Basilar Artery International Cooperation Study
Methods	Randomised, multicentre, open-label, controlled phase III, treatment trial

NCT01717755 *(Continued)*

Participants	Patients aged 18 years and older with CTA- or MRA-confirmed basilar occlusion
Interventions	Patients will be randomised between best medical management with additional intra-arterial therapy versus best medical management alone. Intra-arterial therapy has to be initiated within 6 hours from estimated time of basilar artery occlusion. If used as part of best medical management, intravenous thrombolytic treatment should be started within 4.5 hours of estimated time of stroke onset.
Outcomes	Favourable outcome at day 90 defined as mRS - functional scale of 0 to 3
Starting date	23 October 2012
Contact information	WJ Schonewille, St Antonius Hospital Nieuwegein w.schonewille@antoniusziekenhuis.nl
Notes	

NCT01852201

Study name	PerfusiOn imaging Selection of Ischemic sTroke patIents for endoVascular thErapy (POSITIVE)
Methods	Randomised, multicentre, open-label, controlled phase III, treatment trial
Participants	Age 18 and older (i.e. candidates must have had their 18th birthday) NIHSS ≥ 8 at the time of neuroimaging. Presenting or persistent symptoms within 6 to 12 hours of when groin puncture can be obtained Neuroimaging demonstrates large vessel proximal occlusion (distal Internal Carotid Artery through MCA M1 bifurcation) The operator feels that the stroke can be appropriately treated with traditional endovascular techniques (endovascular mechanical thrombectomy without adjunctive devices such as stents) Patients who are within 6 to 12 hours of symptom onset and who have received IV-tPA without symptom improvement are eligible for this study. Patients presenting earlier than 6 hours should be treated according to local standard of care.
Interventions	Best medical therapy vs intra-arterial treatment plus best medical therapy
Outcomes	modified Rankin Scale score 0 to 2 at 90 days follow-up
Starting date	September 2013
Contact information	Adrian Parker, Medical University of South Carolina, USA parkerad@musc.edu
Notes	

NCT02419781

Study name	Recovery by endovascular salvage for cerebral ultra-acute embolism
Methods	Randomised, open-label, controlled trial
Participants	Acute ischaemic stroke patients who were treated with intravenous r-tPA therapy within 4.5 hours from onset and have persistent occlusion of proximal internal carotid or middle cerebral artery confirmed by cerebral angiography Patients who can receive endovascular treatment within 8 hours after the onset Patients whose DWI-ASPECTS was 5 points and more, or CT-ASPECT was 6 points and more just before cerebral angiography Patients whose NIHSS is between 8 and 29 points Patients who are between 20 and 85 years of age
Interventions	Best medical therapy vs intra-arterial treatment plus best medical therapy
Outcomes	Assessment of modified Rankin Scale shift analysis at 90 days after onset
Starting date	October 2014
Contact information	Shinichi Yoshimura, Hyogo College of Medicine rescue-j@hyo-med.ac.jp
Notes	

NCT03094715

Study name	Efficacy and safety of thrombectomy in stroke with extended lesion and extended time window (TENSION)
Methods	Prospective, open-label, blinded endpoint, randomised controlled trial
Participants	Randomisation within 11 hours after stroke onset (if known) or last seen well Endovascular treatment is expected to be finished within 12 hours after known symptom onset or last seen well by judgement of the interventional neuroradiologist in charge (if stroke onset is known) Patient must demonstrate clinical signs and symptoms attributable to target area of occlusion consistent with the diagnosis of ischaemic stroke, including impairment of the following: language, motor function, sensation, cognition, gaze, and/or vision for at least 30 minutes without relevant improvement Men and women above 18 years of age NIHSS score < 2 Prior to new focal neurological deficit, mRS score was ≤ 2
Interventions	Best medical treatment vs endovascular thrombectomy and best medical care
Outcomes	Clinical outcome: modified Rankin Scale at 90 days
Starting date	March 2017
Contact information	Susanne Bonekamp, DVM, PhD

NCT03094715 *(Continued)*

	susanne.bonekamp@med.uni-heidelberg.de
Notes	

NCT03805308

Study name	The TESLA Trial: Thrombectomy for Emergent Salvage of Large Anterior circulation ischemic stroke
Methods	Prospective, randomised, open-label, blinded endpoint trial
Participants	Patient presenting with symptoms consistent with an acute ischaemic stroke Age 18 to 85 years Imaging evidence of an anterior circulation occlusion of the internal carotid artery terminus or MCA main stem (MCA M1) segment, or both NIHSS score > 6 at the time of randomisation Ability to randomise within 24 hours of stroke onset Pre-stroke mRS score 0 to 1
Interventions	Medical management vs intra-arterial therapy
Outcomes	Utility-weighted 90-day modified Rankin Scale score
Starting date	January 2019
Contact information	Mary S Patterson, MS mspatterson@mercy.com
Notes	

ASPECTS: Alberta Stroke Program Early CT Score
CT: computed tomography
CTA: computed tomography angiography
DWI: diffusion-weighted imaging
IV: intravenous
IV-tPA: intravenous tissue plasminogen activator
MCA: middle cerebral artery
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
r-tPA: recombinant tissue plasminogen activator
sICH: symptomatic intracerebral haemorrhage
TCD: transcranial Doppler
tPA: tissue plasminogen activator

DATA AND ANALYSES

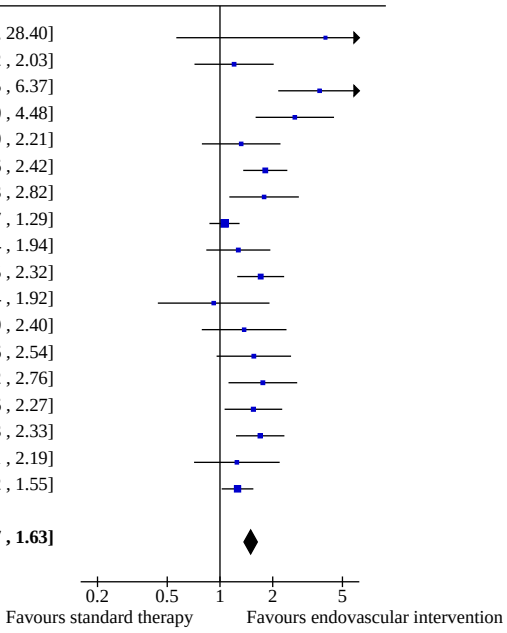
Comparison 1. Favourable functional outcome at end of follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Functional outcome: mRS 0 to 2	18	3715	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.37, 1.63]
1.2 Functional outcome: mRS 0 to 1	18	3632	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.42, 1.82]

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

	Experimental		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
AUST 2005	4	8	1	8	0.2%	4.00 [0.56 , 28.40]	
BEST 2019	22	66	18	65	3.4%	1.20 [0.72 , 2.03]	
DAWN 2018	52	107	13	99	2.5%	3.70 [2.15 , 6.37]	
DEFUSE 2018	41	92	15	90	2.8%	2.67 [1.60 , 4.48]	
EASI 2017	20	40	14	37	2.7%	1.32 [0.79 , 2.21]	
ESCAPE 2015	87	164	43	147	8.5%	1.81 [1.36 , 2.42]	
EXTEND-IA 2015	25	35	14	35	2.6%	1.79 [1.13 , 2.82]	
IMS III 2013	177	415	86	214	21.3%	1.06 [0.87 , 1.29]	
MELT 2007	28	57	22	57	4.1%	1.27 [0.84 , 1.94]	
MR CLEAN 2015	76	233	51	267	8.9%	1.71 [1.25 , 2.32]	
MR RESCUE 2013	12	64	11	54	2.2%	0.92 [0.44 , 1.92]	
PISTE 2016	17	33	12	32	2.3%	1.37 [0.79 , 2.40]	
PROACT 2 1999	48	121	15	59	3.8%	1.56 [0.96 , 2.54]	
RESILIENT 2020	39	111	22	110	4.1%	1.76 [1.12 , 2.76]	
REVASCAT 2015	45	103	29	103	5.4%	1.55 [1.06 , 2.27]	
SWIFT PRIME 2015	59	98	33	93	6.4%	1.70 [1.23 , 2.33]	
THERAPY 2016	19	50	14	46	2.7%	1.25 [0.71 , 2.19]	
THRACE 2016	106	200	85	202	15.9%	1.26 [1.02 , 1.55]	
Total (95% CI)		**1997**		**1718**	**100.0%**	**1.50 [1.37 , 1.63]**	
Total events:	877		498				

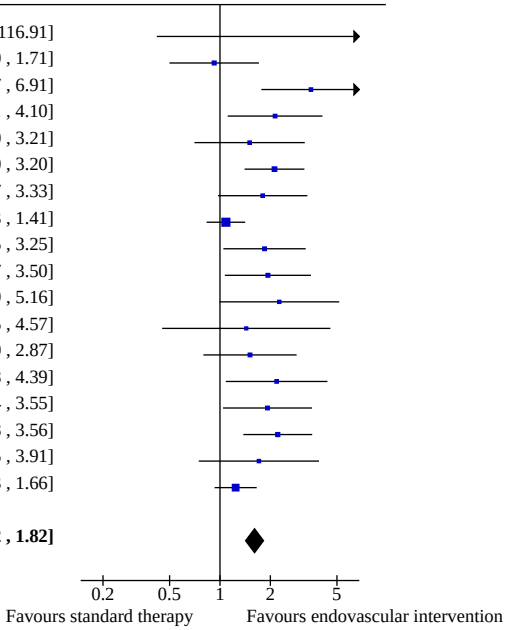
Heterogeneity: Chi² = 38.51, df = 17 (P = 0.002); I² = 56%
Test for overall effect: Z = 9.00 (P < 0.00001)
Test for subgroup differences: Not applicable



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

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AUST 2005	3	8	0	8	0.2%	7.00 [0.42 , 116.91]
BEST 2019	15	66	16	65	5.1%	0.92 [0.50 , 1.71]
DAWN 2018	34	107	9	99	3.0%	3.50 [1.77 , 6.91]
DEFUSE 2018	24	92	11	90	3.5%	2.13 [1.11 , 4.10]
EASI 2017	13	40	8	37	2.6%	1.50 [0.70 , 3.21]
ESCAPE 2015	58	160	25	146	8.3%	2.12 [1.40 , 3.20]
EXTEND-IA 2015	18	35	10	35	3.2%	1.80 [0.97 , 3.33]
IMS III 2013	122	415	58	214	24.3%	1.08 [0.83 , 1.41]
MELT 2007	24	57	13	57	4.1%	1.85 [1.05 , 3.25]
MR CLEAN 2015	27	233	16	267	4.7%	1.93 [1.07 , 3.50]
PISTE 2016	14	33	6	32	1.9%	2.26 [0.99 , 5.16]
PROACT 1 1998	8	26	3	14	1.2%	1.44 [0.45 , 4.57]
PROACT 2 1999	31	121	10	59	4.3%	1.51 [0.80 , 2.87]
RESILIENT 2020	22	111	10	110	3.2%	2.18 [1.08 , 4.39]
REVASCAT 2015	25	103	13	103	4.1%	1.92 [1.04 , 3.55]
SWIFT PRIME 2015	42	98	18	93	5.9%	2.21 [1.38 , 3.56]
THERAPY 2016	13	50	7	46	2.3%	1.71 [0.75 , 3.91]
THRACE 2016	70	200	57	202	18.0%	1.24 [0.93 , 1.66]
Total (95% CI)		**1955**		**1677**	**100.0%**	**1.61 [1.42 , 1.82]**
Total events:	563		290			

Heterogeneity: Chi² = 27.45, df = 17 (P = 0.05); I² = 38%
Test for overall effect: Z = 7.56 (P < 0.00001)
Test for subgroup differences: Not applicable



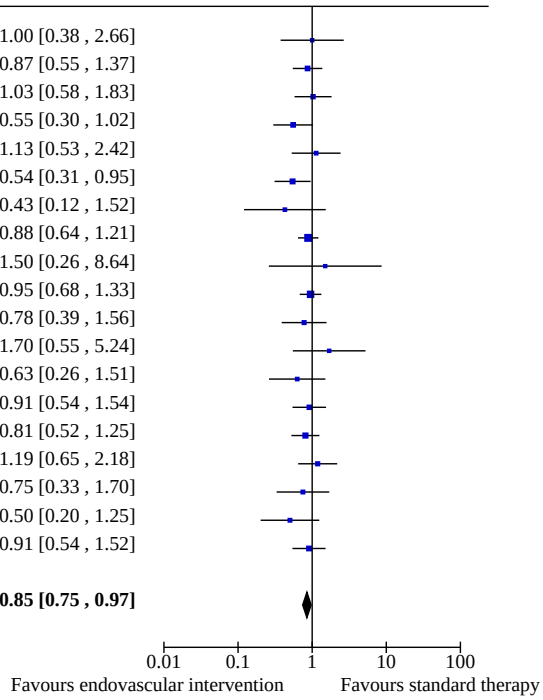
Comparison 2. Death from all causes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Death from all causes at end of follow-up	19	3793	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.75, 0.97]
2.2 Death from all causes within acute phase (first 2 weeks)	3	1243	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.77, 1.47]

Analysis 2.1. Comparison 2: Death from all causes, Outcome 1: Death from all causes at end of follow-up

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AUST 2005	4	8	4	8	1.0%	1.00 [0.38 , 2.66]
BEST 2019	22	66	25	65	6.6%	0.87 [0.55 , 1.37]
DAWN 2018	20	107	18	99	4.9%	1.03 [0.58 , 1.83]
DEFUSE 2018	13	92	23	90	6.1%	0.55 [0.30 , 1.02]
EASI 2017	11	40	9	37	2.4%	1.13 [0.53 , 2.42]
ESCAPE 2015	17	164	28	147	7.7%	0.54 [0.31 , 0.95]
EXTEND-IA 2015	3	35	7	35	1.8%	0.43 [0.12 , 1.52]
IMS III 2013	83	434	48	222	16.5%	0.88 [0.64 , 1.21]
MELT 2007	3	57	2	57	0.5%	1.50 [0.26 , 8.64]
MR CLEAN 2015	49	233	59	267	14.3%	0.95 [0.68 , 1.33]
MR RESCUE 2013	12	64	13	54	3.7%	0.78 [0.39 , 1.56]
PISTE 2016	7	33	4	32	1.1%	1.70 [0.55 , 5.24]
PROACT 1 1998	7	26	6	14	2.0%	0.63 [0.26 , 1.51]
PROACT 2 1999	30	121	16	59	5.6%	0.91 [0.54 , 1.54]
RESILIENT 2020	27	111	33	110	8.6%	0.81 [0.52 , 1.25]
REVASCAT 2015	19	103	16	103	4.2%	1.19 [0.65 , 2.18]
SWIFT PRIME 2015	9	98	12	98	3.1%	0.75 [0.33 , 1.70]
THERAPY 2016	6	50	11	46	3.0%	0.50 [0.20 , 1.25]
THRACE 2016	24	202	27	206	7.0%	0.91 [0.54 , 1.52]
Total (95% CI)		**2044**		**1749**	**100.0%**	**0.85 [0.75 , 0.97]**
Total events:	366		361			

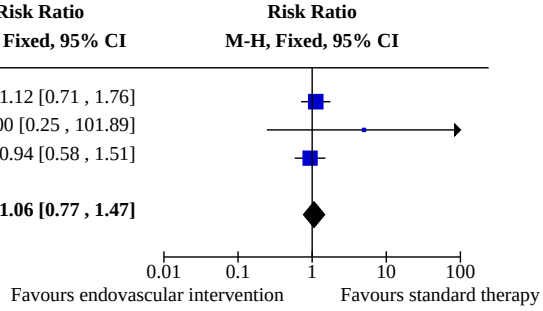
Heterogeneity: Chi² = 12.10, df = 18 (P = 0.84); I² = 0%
Test for overall effect: Z = 2.46 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Death from all causes, Outcome 2: Death from all causes within acute phase (first 2 weeks)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IMS III 2013	52	415	24	214	50.3%	1.12 [0.71 , 1.76]
MELT 2007	2	57	0	57	0.8%	5.00 [0.25 , 101.89]
MR CLEAN 2015	27	233	33	267	48.9%	0.94 [0.58 , 1.51]
Total (95% CI)		**705**		**538**	**100.0%**	**1.06 [0.77 , 1.47]**
Total events:	81		57			

Heterogeneity: Chi² = 1.32, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.72)
Test for subgroup differences: Not applicable



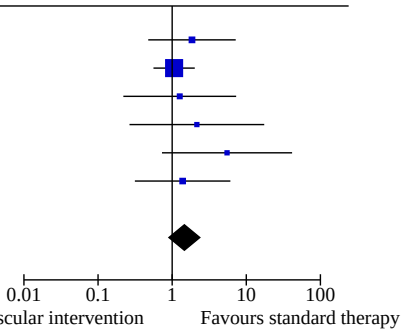
Comparison 3. Symptomatic intracranial haemorrhage (NINDS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Symptomatic intracranial haemorrhage within 24 hours	6	1559	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.91, 2.36]
3.2 Symptomatic intracranial haemorrhage at the end of follow-up	10	1752	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.72, 1.52]

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

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DAWN 2018	6	107	3	99	11.1%	1.85 [0.48 , 7.20]
IMS III 2013	27	434	13	222	61.3%	1.06 [0.56 , 2.02]
MR RESCUE 2013	3	64	2	54	7.7%	1.27 [0.22 , 7.30]
PROACT 1 1998	4	26	1	14	4.6%	2.15 [0.27 , 17.46]
PROACT 2 1999	11	108	1	54	4.8%	5.50 [0.73 , 41.50]
THRACE 2016	4	185	3	192	10.5%	1.38 [0.31 , 6.10]
Total (95% CI)		**924**		**635**	**100.0%**	**1.46 [0.91 , 2.36]**
Total events:	55		23			

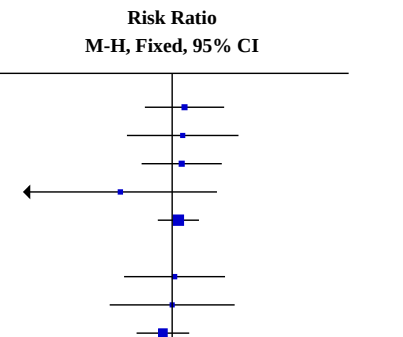
Heterogeneity: Chi² = 2.88, df = 5 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



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

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DEFUSE 2018	6	92	4	90	8.1%	1.47 [0.43 , 5.03]
EASI 2017	3	40	2	37	4.1%	1.39 [0.25 , 7.85]
ESCAPE 2015	6	164	4	147	8.4%	1.34 [0.39 , 4.67]
EXTEND-IA 2015	0	35	2	35	5.0%	0.20 [0.01 , 4.02]
MR CLEAN 2015	18	233	17	267	31.6%	1.21 [0.64 , 2.30]
PISTE 2016	0	33	0	32		Not estimable
PROACT 1 1998	4	26	2	14	5.2%	1.08 [0.22 , 5.17]
REVASCAT 2015	2	103	2	103	4.0%	1.00 [0.14 , 6.96]
SWIFT PRIME 2015	9	98	12	98	23.9%	0.75 [0.33 , 1.70]
THERAPY 2016	4	43	6	62	9.8%	0.96 [0.29 , 3.20]
Total (95% CI)		**867**		**885**	**100.0%**	**1.05 [0.72 , 1.52]**
Total events:	52		51			

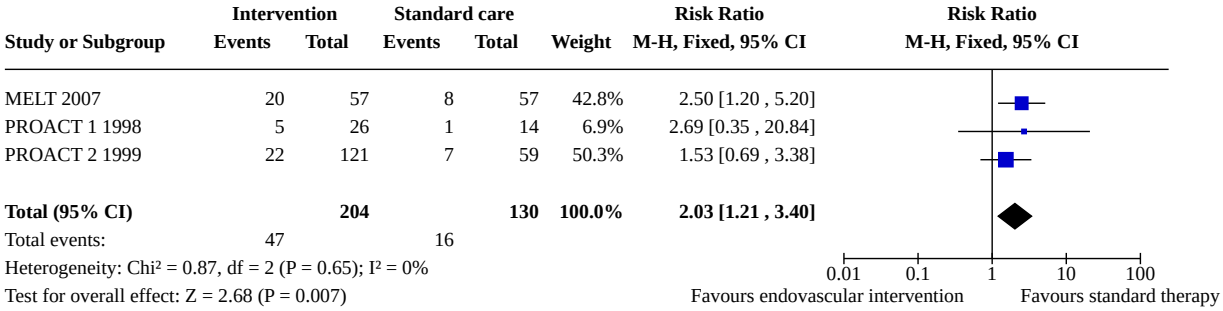
Heterogeneity: Chi² = 2.58, df = 8 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Not applicable



Comparison 4. Neurological outcome at the end of follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Neurological outcome: NIHSS 0 to 1	3	334	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.21, 3.40]

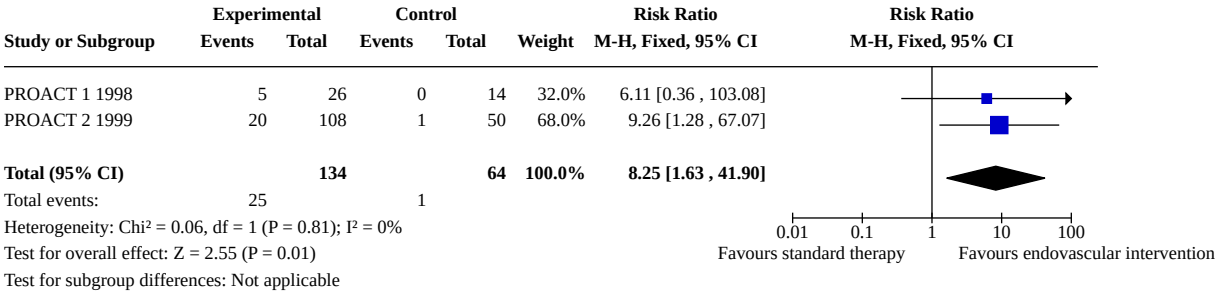
Analysis 4.1. Comparison 4: Neurological outcome at the end of follow-up, Outcome 1: Neurological outcome: NIHSS 0 to 1



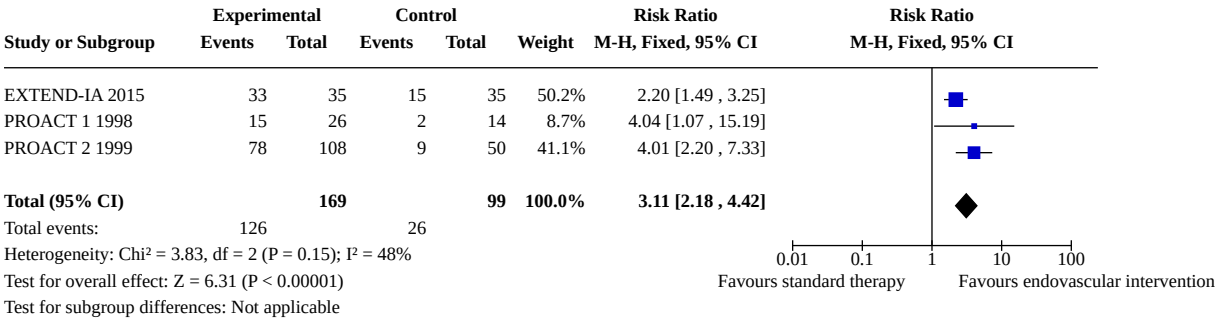
Comparison 5. Degree of recanalisation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Recanalisation: TIMI grade 3	2	198	Risk Ratio (M-H, Fixed, 95% CI)	8.25 [1.63, 41.90]
5.2 Recanalisation: TICI grade 2 and 3	3	268	Risk Ratio (M-H, Fixed, 95% CI)	3.11 [2.18, 4.42]

Analysis 5.1. Comparison 5: Degree of recanalisation, Outcome 1: Recanalisation: TIMI grade 3



Analysis 5.2. Comparison 5: Degree of recanalisation, Outcome 2: Recanalisation: TICI grade 2 and 3



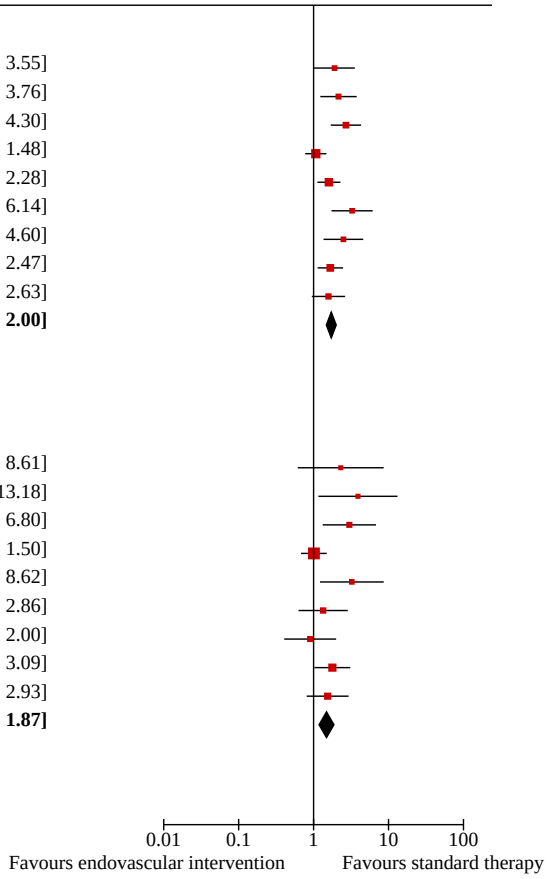
Comparison 6. Subgroup analyses (functional outcome)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Age	9		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.1.1 Younger age	9		Risk Ratio (IV, Fixed, 95% CI)	1.72 [1.48, 2.00]
6.1.2 Older age	9		Risk Ratio (IV, Fixed, 95% CI)	1.49 [1.18, 1.87]
6.2 Sex	7		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.2.1 Men	7		Risk Ratio (IV, Fixed, 95% CI)	1.67 [1.37, 2.04]
6.2.2 Women	7		Risk Ratio (IV, Fixed, 95% CI)	1.63 [1.34, 1.98]
6.3 Stroke severity (NIHSS score)	9		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.3.1 Lower NIHSS score	9		Risk Ratio (IV, Fixed, 95% CI)	1.42 [1.22, 1.66]
6.3.2 Higher NIHSS score	9		Risk Ratio (IV, Fixed, 95% CI)	2.00 [1.57, 2.55]
6.4 Early ischaemic changes on CT according to the Alberta Stroke Program Early CT Score (ASPECTS)	6		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.4.1 Lower ASPECT score	6		Risk Ratio (IV, Fixed, 95% CI)	2.01 [1.53, 2.66]
6.4.2 Higher ASPECT score	6		Risk Ratio (IV, Fixed, 95% CI)	1.39 [1.19, 1.62]
6.5 Mean time to groin puncture or initiation of intra-arterial treatment	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.5.1 Shorter (< 250 minutes)	4	686	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.40, 2.00]
6.5.2 Medium (250 to 300 minutes)	3	1335	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.11, 1.51]
6.5.3 Longer (> 300 minutes)	4	354	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.97, 2.04]
6.6 Intravenous thrombolytic medication	4		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.6.1 Given	4		Risk Ratio (IV, Fixed, 95% CI)	1.95 [1.55, 2.46]
6.6.2 Not given	4		Risk Ratio (IV, Fixed, 95% CI)	2.18 [1.37, 3.47]
6.7 Types of endovascular treatments	17		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.7.1 Trials with participants treated with intra-arterial treatment alone	4	350	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.08, 1.99]
6.7.2 Trials with a majority of participants treated with first-generation mechanical devices	2	747	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.87, 1.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.7.3 Trials with a majority of participants treated with stent retrievers	11	2160	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.59, 2.04]
6.8 Localisation of cerebral artery occlusion	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.8.1 Trials that included both proximal and non-proximal strokes	6	1097	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.99, 1.37]
6.8.2 Trials of that only included proximal occlusion strokes	5	1278	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.47, 1.99]
6.9 Location of occlusion	6		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.9.1 Internal carotid artery	6		Risk Ratio (IV, Fixed, 95% CI)	2.61 [1.88, 3.64]
6.9.2 M1	5		Risk Ratio (IV, Fixed, 95% CI)	1.65 [1.33, 2.04]
6.9.3 M2	1		Risk Ratio (IV, Fixed, 95% CI)	1.35 [0.41, 4.41]
6.10 Penumbra imaging in selecting patients to treatment	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.10.1 Used	3	379	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.22, 2.00]
6.10.2 Not used	8	1996	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.25, 1.59]

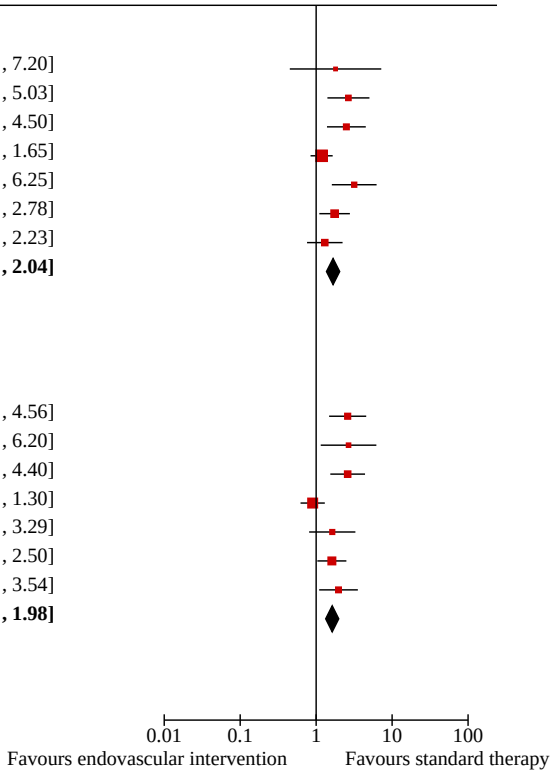
Analysis 6.1. Comparison 6: Subgroup analyses (functional outcome), Outcome 1: Age

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
6.1.1 Younger age				
DAWN 2018	0.64185389	0.31958239	5.9%	1.90 [1.02 , 3.55]
DEFUSE 2018	0.76546784	0.28505224	7.4%	2.15 [1.23 , 3.76]
ESCAPE 2015	0.99325177	0.237430229	10.6%	2.70 [1.70 , 4.30]
IMS III 2013	0.06765865	0.16550175	21.9%	1.07 [0.77 , 1.48]
MR CLEAN 2015	0.47000363	0.180699905	18.4%	1.60 [1.12 , 2.28]
RESILIENT 2020	1.1817272	0.32272279	5.8%	3.26 [1.73 , 6.14]
REVASCAT 2015	0.91629073	0.311104883	6.2%	2.50 [1.36 , 4.60]
SWIFT PRIME 2015	0.51282363	0.199691084	15.0%	1.67 [1.13 , 2.47]
THRACE 2016	0.45742485	0.26073271	8.8%	1.58 [0.95 , 2.63]
Subtotal (95% CI)			**100.0%**	**1.72 [1.48 , 2.00]**
Heterogeneity: Chi² = 18.20, df = 8 (P = 0.02); I² = 56%				
Test for overall effect: Z = 7.02 (P < 0.00001)				
6.1.2 Older age				
DAWN 2018	0.83290912	0.67322891	3.0%	2.30 [0.61 , 8.61]
DEFUSE 2018	1.36353737	0.62009473	3.5%	3.91 [1.16 , 13.18]
ESCAPE 2015	1.0986	0.4175	7.8%	3.00 [1.32 , 6.80]
IMS III 2013	0.00995033	0.20179325	33.3%	1.01 [0.68 , 1.50]
MR CLEAN 2015	1.17557333	0.49924069	5.4%	3.24 [1.22 , 8.62]
RESILIENT 2020	0.29266961	0.38593293	9.1%	1.34 [0.63 , 2.86]
REVASCAT 2015	-0.10536	0.407	8.2%	0.90 [0.41 , 2.00]
SWIFT PRIME 2015	0.57661336	0.281407003	17.1%	1.78 [1.03 , 3.09]
THRACE 2016	0.43178242	0.32799068	12.6%	1.54 [0.81 , 2.93]
Subtotal (95% CI)			**100.0%**	**1.49 [1.18 , 1.87]**
Heterogeneity: Chi² = 13.80, df = 8 (P = 0.09); I² = 42%				
Test for overall effect: Z = 3.41 (P = 0.0007)				
Test for subgroup differences: Chi² = 1.10, df = 1 (P = 0.29), I² = 9.2%				



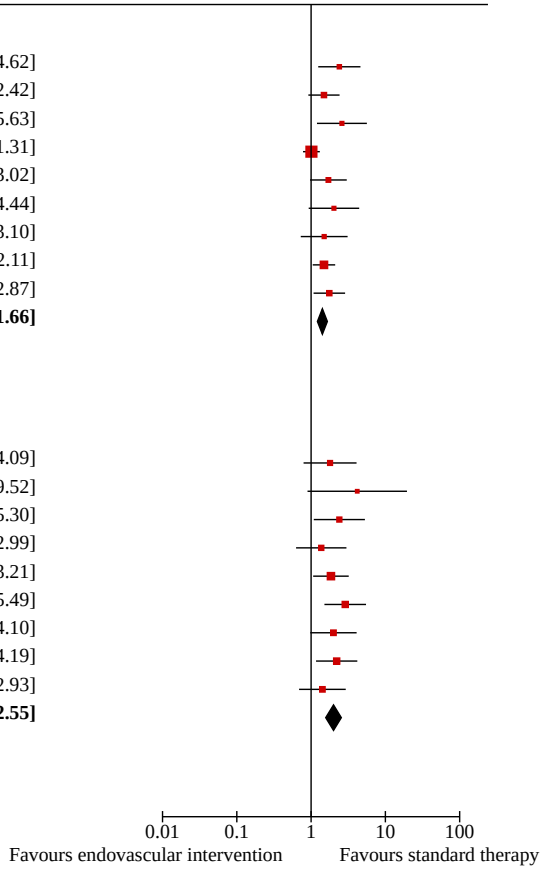
Analysis 6.2. Comparison 6: Subgroup analyses (functional outcome), Outcome 2: Sex

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
6.2.1 Men				
DAWN 2018	0.58778666	0.70729304	2.1%	1.80 [0.45 , 7.20]
DEFUSE 2018	0.97832612	0.32495316	9.8%	2.66 [1.41 , 5.03]
ESCAPE 2015	0.91629073	0.29989116	11.5%	2.50 [1.39 , 4.50]
IMS III 2013	0.16551444	0.17105145	35.5%	1.18 [0.84 , 1.65]
RESILIENT 2020	1.15373159	0.34600696	8.7%	3.17 [1.61 , 6.25]
SWIFT PRIME 2015	0.55961579	0.23614038	18.6%	1.75 [1.10 , 2.78]
THRACE 2016	0.26236426	0.27460164	13.8%	1.30 [0.76 , 2.23]
Subtotal (95% CI)			**100.0%**	**1.67 [1.37 , 2.04]**
Heterogeneity: Chi² = 12.30, df = 6 (P = 0.06); I² = 51%				
Test for overall effect: Z = 5.04 (P < 0.00001)				
6.2.2 Women				
DAWN 2018	0.95551145	0.28671686	12.3%	2.60 [1.48 , 4.56]
DEFUSE 2018	0.98207847	0.43020381	5.5%	2.67 [1.15 , 6.20]
ESCAPE 2015	0.95551145	0.26841484	14.1%	2.60 [1.54 , 4.40]
IMS III 2013	-0.10536052	0.18761468	28.8%	0.90 [0.62 , 1.30]
RESILIENT 2020	0.48858001	0.35755321	7.9%	1.63 [0.81 , 3.29]
SWIFT PRIME 2015	0.47623418	0.22451865	20.1%	1.61 [1.04 , 2.50]
THRACE 2016	0.67803354	0.2988871	11.3%	1.97 [1.10 , 3.54]
Subtotal (95% CI)			**100.0%**	**1.63 [1.34 , 1.98]**
Heterogeneity: Chi² = 17.42, df = 6 (P = 0.008); I² = 66%				
Test for overall effect: Z = 4.84 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%				



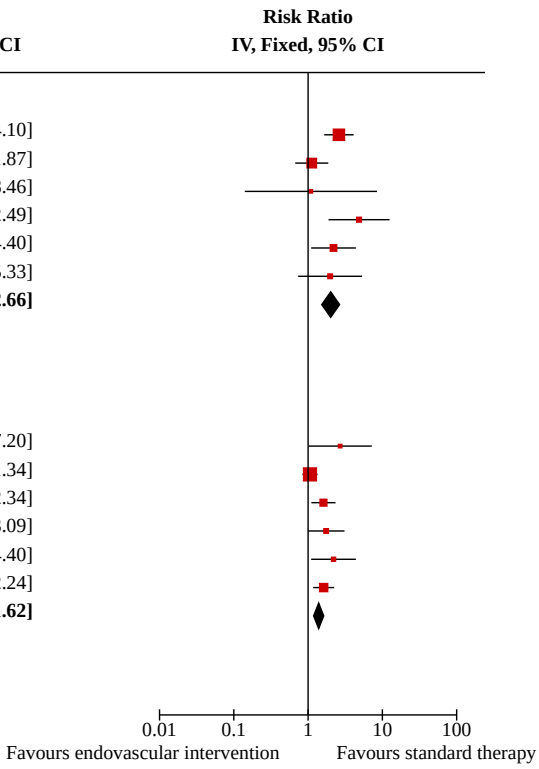
Analysis 6.3. Comparison 6: Subgroup analyses (functional outcome), Outcome 3: Stroke severity (NIHSS score)

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
6.3.1 Lower NIHSS score				
DAWN 2018	0.87546874	0.33375837	5.5%	2.40 [1.25 , 4.62]
DEFUSE 2018	0.39877612	0.24672172	10.1%	1.49 [0.92 , 2.42]
ESCAPE 2015	0.95551145	0.394484637	4.0%	2.60 [1.20 , 5.63]
IMS III 2013	0.00995033	0.13269225	35.1%	1.01 [0.78 , 1.31]
MR CLEAN 2015	0.53649337	0.290185439	7.3%	1.71 [0.97 , 3.02]
RESILIENT 2020	0.70803579	0.39935581	3.9%	2.03 [0.93 , 4.44]
REVASCAT 2015	0.40546511	0.370376022	4.5%	1.50 [0.73 , 3.10]
SWIFT PRIME 2015	0.39877612	0.177506034	19.6%	1.49 [1.05 , 2.11]
THRACE 2016	0.56531381	0.24932423	9.9%	1.76 [1.08 , 2.87]
Subtotal (95% CI)			**100.0%**	**1.42 [1.22 , 1.66]**
Heterogeneity: Chi² = 13.50, df = 8 (P = 0.10); I² = 41%				
Test for overall effect: Z = 4.45 (P < 0.00001)				
6.3.2 Higher NIHSS score				
DAWN 2018	0.58778666	0.41893565	8.7%	1.80 [0.79 , 4.09]
DEFUSE 2018	1.43031125	0.78639075	2.5%	4.18 [0.89 , 19.52]
ESCAPE 2015	0.87546874	0.404203104	9.3%	2.40 [1.09 , 5.30]
IMS III 2013	0.31481074	0.39819523	9.6%	1.37 [0.63 , 2.99]
MR CLEAN 2015	0.61518564	0.281165968	19.2%	1.85 [1.07 , 3.21]
RESILIENT 2020	1.05779029	0.32882537	14.0%	2.88 [1.51 , 5.49]
REVASCAT 2015	0.69314718	0.366244792	11.3%	2.00 [0.98 , 4.10]
SWIFT PRIME 2015	0.79299252	0.326381744	14.3%	2.21 [1.17 , 4.19]
THRACE 2016	0.35065687	0.36889441	11.2%	1.42 [0.69 , 2.93]
Subtotal (95% CI)			**100.0%**	**2.00 [1.57 , 2.55]**
Heterogeneity: Chi² = 4.31, df = 8 (P = 0.83); I² = 0%				
Test for overall effect: Z = 5.64 (P < 0.00001)				
Test for subgroup differences: Chi² = 5.58, df = 1 (P = 0.02), I² = 82.1%				



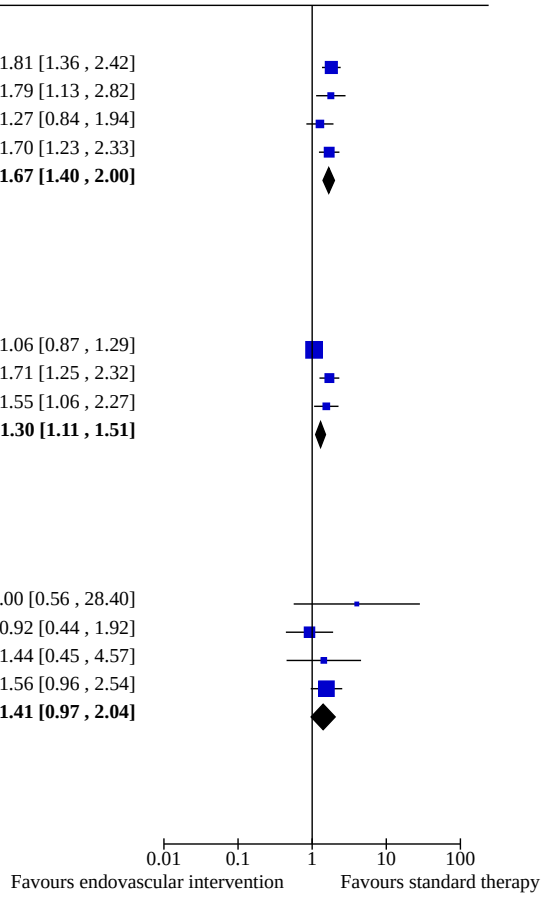
Analysis 6.4. Comparison 6: Subgroup analyses (functional outcome), Outcome 4: Early ischaemic changes on CT according to the Alberta Stroke Program Early CT Score (ASPECTS)

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
6.4.1 Lower ASPECT score				
ESCAPE 2015	0.95551145	0.232385474	36.8%	2.60 [1.65 , 4.10]
IMS III 2013	0.11332869	0.26153558	29.1%	1.12 [0.67 , 1.87]
MR CLEAN 2015	0.0861777	1.045495652	1.8%	1.09 [0.14 , 8.46]
RESILIENT 2020	1.5789787	0.48246218	8.5%	4.85 [1.88 , 12.49]
REVASCAT 2015	0.78845736	0.353646521	15.9%	2.20 [1.10 , 4.40]
SWIFT PRIME 2015	0.68309684	0.505231833	7.8%	1.98 [0.74 , 5.33]
Subtotal (95% CI)			**100.0%**	**2.01 [1.53 , 2.66]**
Heterogeneity: Chi² = 9.97, df = 5 (P = 0.08); I² = 50%				
Test for overall effect: Z = 4.96 (P < 0.00001)				
6.4.2 Higher ASPECT score				
ESCAPE 2015	0.99325177	0.500423088	2.5%	2.70 [1.01 , 7.20]
IMS III 2013	0.05826891	0.1195922	44.3%	1.06 [0.84 , 1.34]
MR CLEAN 2015	0.47623418	0.190773852	17.4%	1.61 [1.11 , 2.34]
RESILIENT 2020	0.55961579	0.29036261	7.5%	1.75 [0.99 , 3.09]
REVASCAT 2015	0.78845736	0.353646521	5.1%	2.20 [1.10 , 4.40]
SWIFT PRIME 2015	0.48242615	0.165331488	23.2%	1.62 [1.17 , 2.24]
Subtotal (95% CI)			**100.0%**	**1.39 [1.19 , 1.62]**
Heterogeneity: Chi² = 10.66, df = 5 (P = 0.06); I² = 53%				
Test for overall effect: Z = 4.12 (P < 0.0001)				
Test for subgroup differences: Chi² = 5.29, df = 1 (P = 0.02), I² = 81.1%				



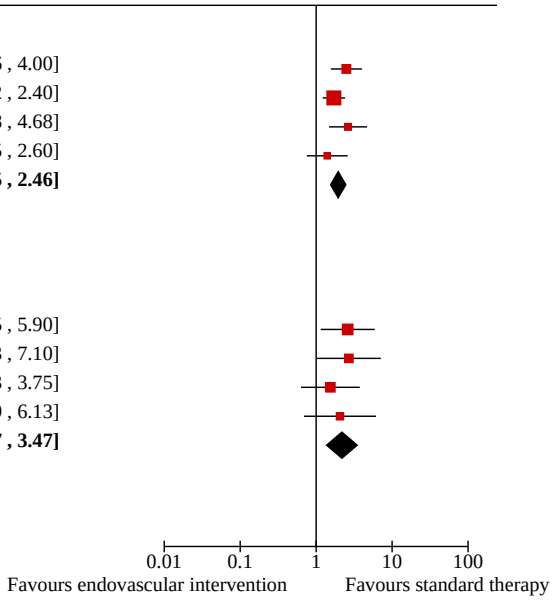
Analysis 6.5. Comparison 6: Subgroup analyses (functional outcome), Outcome 5: Mean time to groin puncture or initiation of intra-arterial treatment

Study or Subgroup	Intervention Events	Intervention Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.5.1 Shorter (< 250 minutes)						
ESCAPE 2015	87	164	43	147	39.4%	1.81 [1.36 , 2.42]
EXTEND-IA 2015	25	35	14	35	12.2%	1.79 [1.13 , 2.82]
MELT 2007	28	57	22	57	19.1%	1.27 [0.84 , 1.94]
SWIFT PRIME 2015	59	98	33	93	29.4%	1.70 [1.23 , 2.33]
Subtotal (95% CI)		**354**		**332**	**100.0%**	**1.67 [1.40 , 2.00]**
Total events:	199		112			
Heterogeneity: Chi² = 2.01, df = 3 (P = 0.57); I² = 0%						
Test for overall effect: Z = 5.71 (P < 0.00001)						
6.5.2 Medium (250 to 300 minutes)						
IMS III 2013	177	415	86	214	59.7%	1.06 [0.87 , 1.29]
MR CLEAN 2015	76	233	51	267	25.0%	1.71 [1.25 , 2.32]
REVASCAT 2015	45	103	29	103	15.3%	1.55 [1.06 , 2.27]
Subtotal (95% CI)		**751**		**584**	**100.0%**	**1.30 [1.11 , 1.51]**
Total events:	298		166			
Heterogeneity: Chi² = 7.87, df = 2 (P = 0.02); I² = 75%						
Test for overall effect: Z = 3.35 (P = 0.0008)						
6.5.3 Longer (> 300 minutes)						
AUST 2005	4	8	1	8	2.7%	4.00 [0.56 , 28.40]
MR RESCUE 2013	12	64	11	54	32.3%	0.92 [0.44 , 1.92]
PROACT 1 1998	8	26	3	14	10.5%	1.44 [0.45 , 4.57]
PROACT 2 1999	48	121	15	59	54.5%	1.56 [0.96 , 2.54]
Subtotal (95% CI)		**219**		**135**	**100.0%**	**1.41 [0.97 , 2.04]**
Total events:	72		30			
Heterogeneity: Chi² = 2.55, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.80 (P = 0.07)						
Test for subgroup differences: Chi² = 4.56, df = 2 (P = 0.10), I² = 56.2%						



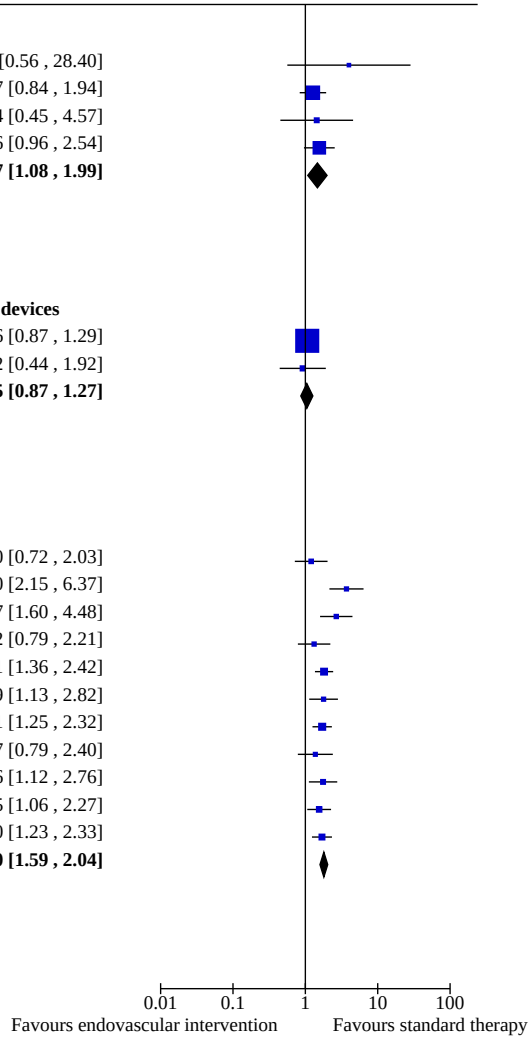
Analysis 6.6. Comparison 6: Subgroup analyses (functional outcome), Outcome 6: Intravenous thrombolytic medication

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
6.6.1 Given				
ESCAPE 2015	0.91629073	0.23979777	24.0%	2.50 [1.56 , 4.00]
MR CLEAN 2015	0.53649337	0.17294662	46.2%	1.71 [1.22 , 2.40]
RESILIENT 2020	0.96698385	0.29423227	16.0%	2.63 [1.48 , 4.68]
REVASCAT 2015	0.33647224	0.3158633	13.8%	1.40 [0.75 , 2.60]
Subtotal (95% CI)			**100.0%**	**1.95 [1.55 , 2.46]**
Heterogeneity: Chi² = 3.78, df = 3 (P = 0.29); I² = 21%				
Test for overall effect: Z = 5.69 (P < 0.00001)				
6.6.2 Not given				
ESCAPE 2015	0.95551145	0.4180821	32.0%	2.60 [1.15 , 5.90]
MR CLEAN 2015	0.99325177	0.49328725	23.0%	2.70 [1.03 , 7.10]
RESILIENT 2020	0.43178242	0.45436762	27.1%	1.54 [0.63 , 3.75]
REVASCAT 2015	0.722270598	0.55637182	18.0%	2.06 [0.69 , 6.13]
Subtotal (95% CI)			**100.0%**	**2.18 [1.37 , 3.47]**
Heterogeneity: Chi² = 0.96, df = 3 (P = 0.81); I² = 0%				
Test for overall effect: Z = 3.30 (P = 0.0010)				
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%				



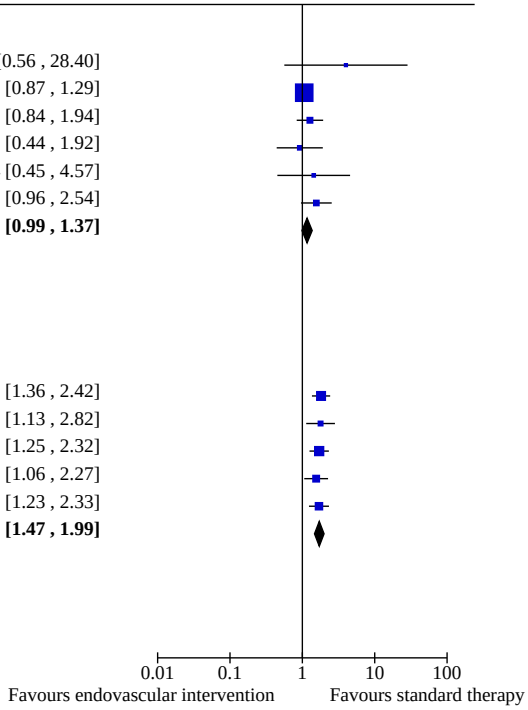
Analysis 6.7. Comparison 6: Subgroup analyses (functional outcome), Outcome 7: Types of endovascular treatments

Study or Subgroup	Intervention Events	Intervention Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.7.1 Trials with participants treated with intra-arterial treatment alone						
AUST 2005	4	8	1	8	2.1%	4.00 [0.56 , 28.40]
MELT 2007	28	57	22	57	46.7%	1.27 [0.84 , 1.94]
PROACT 1 1998	8	26	3	14	8.3%	1.44 [0.45 , 4.57]
PROACT 2 1999	48	121	15	59	42.8%	1.56 [0.96 , 2.54]
Subtotal (95% CI)		**212**		**138**	**100.0%**	**1.47 [1.08 , 1.99]**
Total events:	88		41			
Heterogeneity: Chi² = 1.51, df = 3 (P = 0.68); I² = 0%						
Test for overall effect: Z = 2.45 (P = 0.01)						
6.7.2 Trials with a majority of participants treated with first-generation mechanical devices						
IMS III 2013	177	415	86	214	90.5%	1.06 [0.87 , 1.29]
MR RESCUE 2013	12	64	11	54	9.5%	0.92 [0.44 , 1.92]
Subtotal (95% CI)		**479**		**268**	**100.0%**	**1.05 [0.87 , 1.27]**
Total events:	189		97			
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
6.7.3 Trials with a majority of participants treated with stent retrievers						
BEST 2019	22	66	18	65	6.8%	1.20 [0.72 , 2.03]
DAWN 2018	52	107	13	99	5.1%	3.70 [2.15 , 6.37]
DEFUSE 2018	41	92	15	90	5.7%	2.67 [1.60 , 4.48]
EASI 2017	20	40	14	37	5.5%	1.32 [0.79 , 2.21]
ESCAPE 2015	87	164	43	147	17.1%	1.81 [1.36 , 2.42]
EXTEND-IA 2015	25	35	14	35	5.3%	1.79 [1.13 , 2.82]
MR CLEAN 2015	76	233	51	267	17.9%	1.71 [1.25 , 2.32]
PISTE 2016	17	33	12	32	4.6%	1.37 [0.79 , 2.40]
RESILIENT 2020	39	111	22	110	8.3%	1.76 [1.12 , 2.76]
REVASCAT 2015	45	103	29	103	10.9%	1.55 [1.06 , 2.27]
SWIFT PRIME 2015	59	98	33	93	12.8%	1.70 [1.23 , 2.33]
Subtotal (95% CI)		**1082**		**1078**	**100.0%**	**1.80 [1.59 , 2.04]**
Total events:	483		264			
Heterogeneity: Chi² = 14.48, df = 10 (P = 0.15); I² = 31%						
Test for overall effect: Z = 9.38 (P < 0.00001)						
Test for subgroup differences: Chi² = 21.81, df = 2 (P < 0.0001), I² = 90.8%						



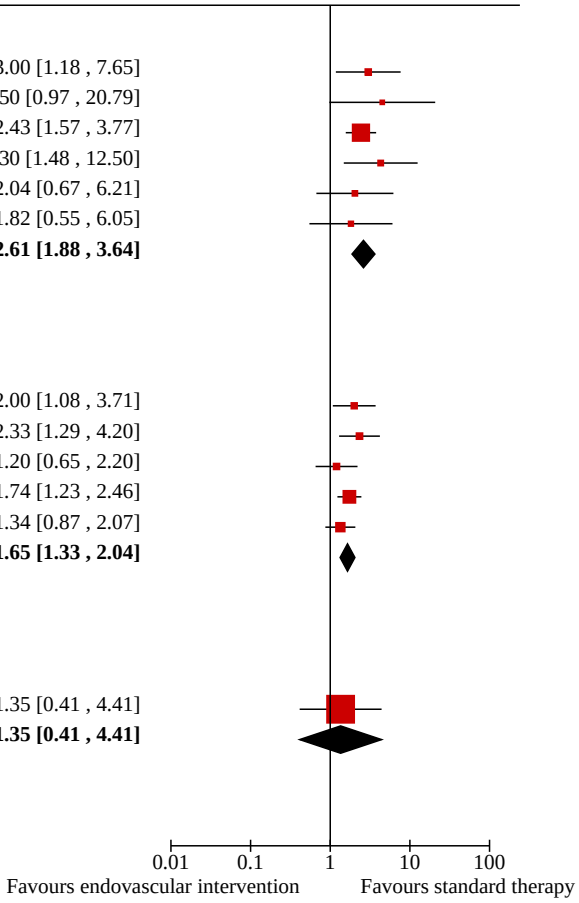
Analysis 6.8. Comparison 6: Subgroup analyses (functional outcome), Outcome 8: Localisation of cerebral artery occlusion

Study or Subgroup	Treatment Events	Treatment Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.8.1 Trials that included both proximal and non-proximal strokes						
AUST 2005	4	8	1	8	0.6%	4.00 [0.56 , 28.40]
IMS III 2013	177	415	86	214	65.8%	1.06 [0.87 , 1.29]
MELT 2007	28	57	22	57	12.8%	1.27 [0.84 , 1.94]
MR RESCUE 2013	12	64	11	54	6.9%	0.92 [0.44 , 1.92]
PROACT 1 1998	8	26	3	14	2.3%	1.44 [0.45 , 4.57]
PROACT 2 1999	48	121	15	59	11.7%	1.56 [0.96 , 2.54]
Subtotal (95% CI)		**691**		**406**	**100.0%**	**1.16 [0.99 , 1.37]**
Total events:	277		138			
Heterogeneity: Chi² = 4.43, df = 5 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.82 (P = 0.07)						
6.8.2 Trials of that only included proximal occlusion strokes						
ESCAPE 2015	87	164	43	147	26.7%	1.81 [1.36 , 2.42]
EXTEND-IA 2015	25	35	14	35	8.2%	1.79 [1.13 , 2.82]
MR CLEAN 2015	76	233	51	267	28.0%	1.71 [1.25 , 2.32]
REVASCAT 2015	45	103	29	103	17.1%	1.55 [1.06 , 2.27]
SWIFT PRIME 2015	59	98	33	93	19.9%	1.70 [1.23 , 2.33]
Subtotal (95% CI)		**633**		**645**	**100.0%**	**1.71 [1.47 , 1.99]**
Total events:	292		170			
Heterogeneity: Chi² = 0.45, df = 4 (P = 0.98); I² = 0%						
Test for overall effect: Z = 6.96 (P < 0.00001)						
Test for subgroup differences: Chi² = 11.72, df = 1 (P = 0.0006), I² = 91.5%						

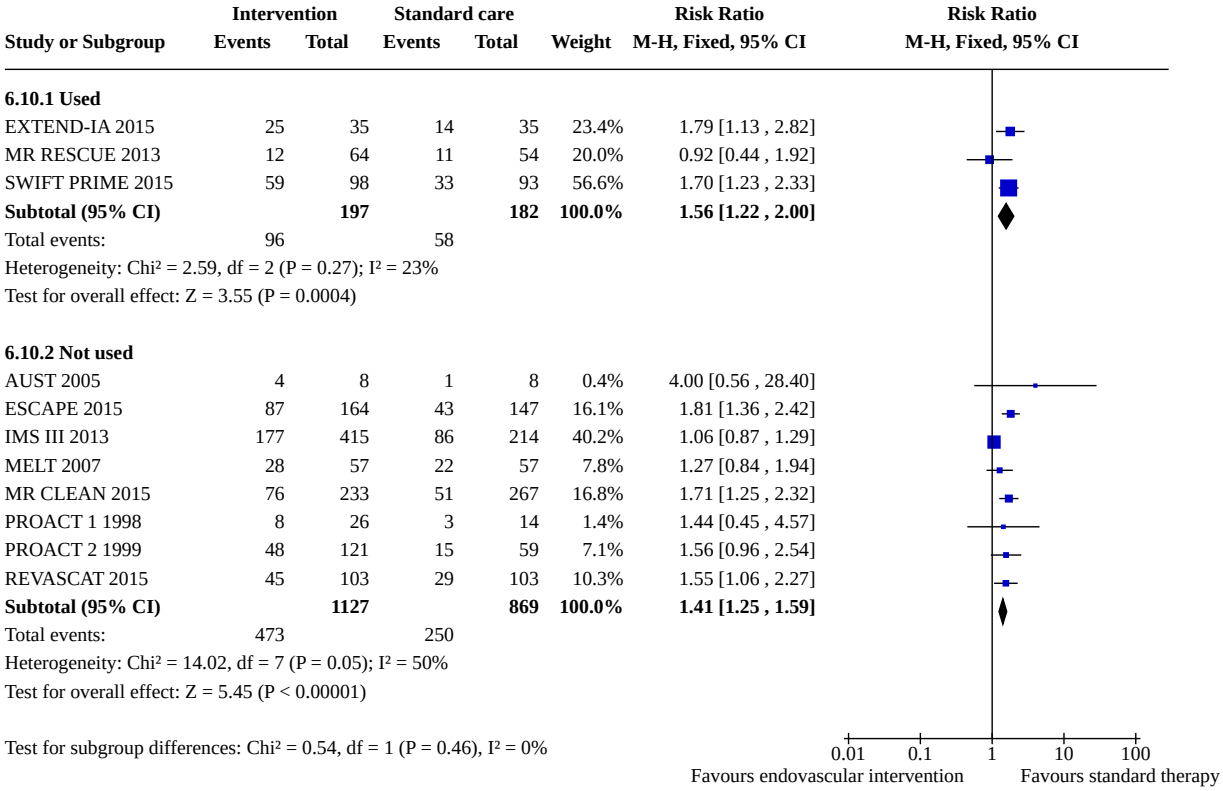


Analysis 6.9. Comparison 6: Subgroup analyses (functional outcome), Outcome 9: Location of occlusion

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
6.9.1 Internal carotid artery				
DAWN 2018	1.09861229	0.47750056	12.5%	3.00 [1.18 , 7.65]
DEFUSE 2018	1.5040774	0.78082467	4.7%	4.50 [0.97 , 20.79]
MR CLEAN 2015	0.88789126	0.224073339	56.8%	2.43 [1.57 , 3.77]
REVASCAT 2015	1.45861502	0.544445725	9.6%	4.30 [1.48 , 12.50]
SWIFT PRIME 2015	0.71294981	0.567964841	8.8%	2.04 [0.67 , 6.21]
THRACE 2016	0.5988365	0.6125499	7.6%	1.82 [0.55 , 6.05]
Subtotal (95% CI)			**100.0%**	**2.61 [1.88 , 3.64]**
Heterogeneity: Chi² = 2.05, df = 5 (P = 0.84); I² = 0%				
Test for overall effect: Z = 5.69 (P < 0.00001)				
6.9.2 M1				
DAWN 2018	0.69314718	0.31550067	12.0%	2.00 [1.08 , 3.71]
DEFUSE 2018	0.845868268	0.30052513	13.2%	2.33 [1.29 , 4.20]
REVASCAT 2015	0.18232156	0.309252961	12.4%	1.20 [0.65 , 2.20]
SWIFT PRIME 2015	0.55388511	0.176671549	38.1%	1.74 [1.23 , 2.46]
THRACE 2016	0.29266961	0.22112517	24.3%	1.34 [0.87 , 2.07]
Subtotal (95% CI)			**100.0%**	**1.65 [1.33 , 2.04]**
Heterogeneity: Chi² = 3.73, df = 4 (P = 0.44); I² = 0%				
Test for overall effect: Z = 4.58 (P < 0.00001)				
6.9.3 M2				
SWIFT PRIME 2015	0.30010459	0.603964335	100.0%	1.35 [0.41 , 4.41]
Subtotal (95% CI)			**100.0%**	**1.35 [0.41 , 4.41]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.50 (P = 0.62)				



Analysis 6.10. Comparison 6: Subgroup analyses (functional outcome), Outcome 10: Penumbra imaging in selecting patients to treatment

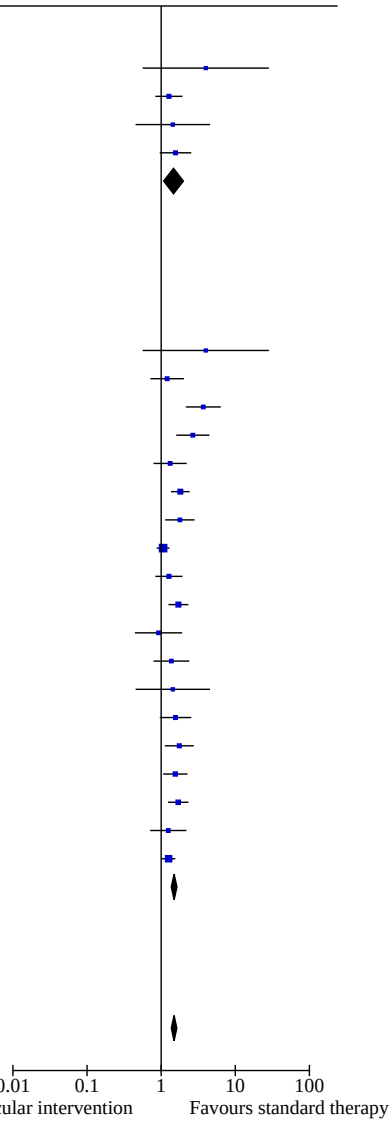


Comparison 7. Sensitivity analyses (functional outcome, mRS 0 to 2, or mRS 0 to 1 if data not available for mRS 0 to 2))

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Trials included in the previous review vs trials included in the current review	19	4105	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.37, 1.62]
7.1.1 Trials included in the previous review	4	350	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.08, 1.99]
7.1.2 Trials included in the current review	19	3755	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.37, 1.63]
7.2 Trials that included all planned participants vs trials stopped early	19	3533	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.40, 1.69]
7.2.1 Trials that included all planned participants	3	798	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.22, 1.98]
7.2.2 Trials stopped early	16	2735	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.39, 1.70]
7.3 Functional outcome: mRS 0 to 2 (random effects)	18	3715	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.33, 1.78]

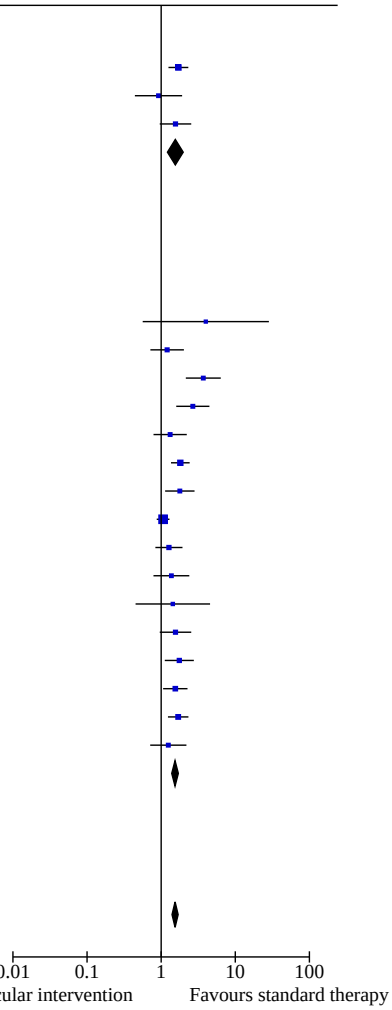
Analysis 7.1. Comparison 7: Sensitivity analyses (functional outcome, mRS 0 to 2, or mRS 0 to 1 if data not available for mRS 0 to 2)), Outcome 1: Trials included in the previous review vs trials included in the current review

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 Trials included in the previous review						
AUST 2005	4	8	1	8	0.2%	4.00 [0.56 , 28.40]
MELT 2007	28	57	22	57	3.8%	1.27 [0.84 , 1.94]
PROACT 1 1998	8	26	3	14	0.7%	1.44 [0.45 , 4.57]
PROACT 2 1999	48	121	15	59	3.5%	1.56 [0.96 , 2.54]
Subtotal (95% CI)		**212**		**138**	**8.1%**	**1.47 [1.08 , 1.99]**
Total events:	88		41			
Heterogeneity: Chi² = 1.51, df = 3 (P = 0.68); I² = 0%						
Test for overall effect: Z = 2.45 (P = 0.01)						
7.1.2 Trials included in the current review						
AUST 2005	4	8	1	8	0.2%	4.00 [0.56 , 28.40]
BEST 2019	22	66	18	65	3.1%	1.20 [0.72 , 2.03]
DAWN 2018	52	107	13	99	2.3%	3.70 [2.15 , 6.37]
DEFUSE 2018	41	92	15	90	2.6%	2.67 [1.60 , 4.48]
EASI 2017	20	40	14	37	2.5%	1.32 [0.79 , 2.21]
ESCAPE 2015	87	164	43	147	7.8%	1.81 [1.36 , 2.42]
EXTEND-IA 2015	25	35	14	35	2.4%	1.79 [1.13 , 2.82]
IMS III 2013	177	415	86	214	19.4%	1.06 [0.87 , 1.29]
MELT 2007	28	57	22	57	3.8%	1.27 [0.84 , 1.94]
MR CLEAN 2015	76	233	51	267	8.1%	1.71 [1.25 , 2.32]
MR RESCUE 2013	12	64	11	54	2.0%	0.92 [0.44 , 1.92]
PISTE 2016	17	33	12	32	2.1%	1.37 [0.79 , 2.40]
PROACT 1 1998	8	26	3	14	0.7%	1.44 [0.45 , 4.57]
PROACT 2 1999	48	121	15	59	3.5%	1.56 [0.96 , 2.54]
RESILIENT 2020	39	111	22	110	3.8%	1.76 [1.12 , 2.76]
REVASCAT 2015	45	103	29	103	5.0%	1.55 [1.06 , 2.27]
SWIFT PRIME 2015	59	98	33	93	5.8%	1.70 [1.23 , 2.33]
THERAPY 2016	19	50	14	46	2.5%	1.25 [0.71 , 2.19]
THRACE 2016	106	200	85	202	14.5%	1.26 [1.02 , 1.55]
Subtotal (95% CI)		**2023**		**1732**	**91.9%**	**1.50 [1.37 , 1.63]**
Total events:	885		501			
Heterogeneity: Chi² = 38.50, df = 18 (P = 0.003); I² = 53%						
Test for overall effect: Z = 9.02 (P < 0.00001)						
Total (95% CI)		**2235**		**1870**	**100.0%**	**1.49 [1.37 , 1.62]**
Total events:	973		542			
Heterogeneity: Chi² = 40.01, df = 22 (P = 0.01); I² = 45%						
Test for overall effect: Z = 9.34 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%						



Analysis 7.2. Comparison 7: Sensitivity analyses (functional outcome, mRS 0 to 2, or mRS 0 to 1 if data not available for mRS 0 to 2)), Outcome 2: Trials that included all planned participants vs trials stopped early

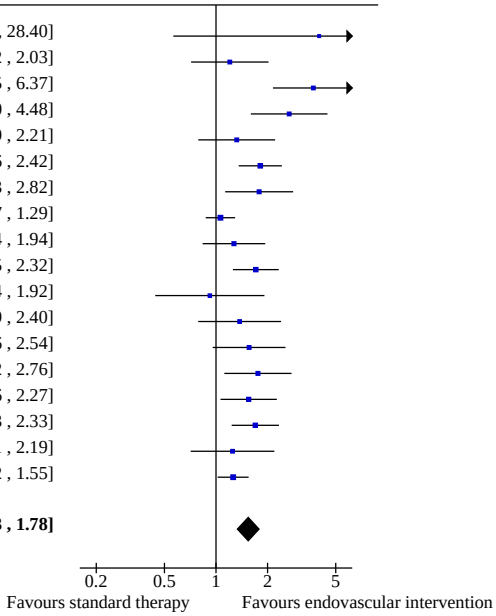
Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 Trials that included all planned participants						
MR CLEAN 2015	76	233	51	267	10.1%	1.71 [1.25 , 2.32]
MR RESCUE 2013	12	64	11	54	2.5%	0.92 [0.44 , 1.92]
PROACT 2 1999	48	121	15	59	4.3%	1.56 [0.96 , 2.54]
Subtotal (95% CI)		**418**		**380**	**16.8%**	**1.55 [1.22 , 1.98]**
Total events:	136		77			
Heterogeneity: Chi² = 2.32, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 3.52 (P = 0.0004)						
7.2.2 Trials stopped early						
AUST 2005	4	8	1	8	0.2%	4.00 [0.56 , 28.40]
BEST 2019	22	66	18	65	3.8%	1.20 [0.72 , 2.03]
DAWN 2018	52	107	13	99	2.9%	3.70 [2.15 , 6.37]
DEFUSE 2018	41	92	15	90	3.2%	2.67 [1.60 , 4.48]
EASI 2017	20	40	14	37	3.1%	1.32 [0.79 , 2.21]
ESCAPE 2015	87	164	43	147	9.6%	1.81 [1.36 , 2.42]
EXTEND-IA 2015	25	35	14	35	3.0%	1.79 [1.13 , 2.82]
IMS III 2013	177	415	86	214	24.0%	1.06 [0.87 , 1.29]
MELT 2007	28	57	22	57	4.7%	1.27 [0.84 , 1.94]
PISTE 2016	17	33	12	32	2.6%	1.37 [0.79 , 2.40]
PROACT 1 1998	8	26	3	14	0.8%	1.44 [0.45 , 4.57]
RESILIENT 2020	48	121	15	59	4.3%	1.56 [0.96 , 2.54]
REVASCAT 2015	39	111	22	110	4.7%	1.76 [1.12 , 2.76]
SWIFT PRIME 2015	45	103	29	103	6.1%	1.55 [1.06 , 2.27]
THERAPY 2016	59	98	33	93	7.2%	1.70 [1.23 , 2.33]
THRACE 2016	19	50	14	46	3.1%	1.25 [0.71 , 2.19]
Subtotal (95% CI)		**1526**		**1209**	**83.2%**	**1.54 [1.39 , 1.70]**
Total events:	691		354			
Heterogeneity: Chi² = 33.92, df = 15 (P = 0.003); I² = 56%						
Test for overall effect: Z = 8.27 (P < 0.00001)						
Total (95% CI)		**1944**		**1589**	**100.0%**	**1.54 [1.40 , 1.69]**
Total events:	827		431			
Heterogeneity: Chi² = 36.29, df = 18 (P = 0.006); I² = 50%						
Test for overall effect: Z = 8.98 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						



Analysis 7.3. Comparison 7: Sensitivity analyses (functional outcome, mRS 0 to 2, or mRS 0 to 1 if data not available for mRS 0 to 2)), Outcome 3: Functional outcome: mRS 0 to 2 (random effects)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AUST 2005	4	8	1	8	0.5%	4.00 [0.56 , 28.40]
BEST 2019	22	66	18	65	4.6%	1.20 [0.72 , 2.03]
DAWN 2018	52	107	13	99	4.4%	3.70 [2.15 , 6.37]
DEFUSE 2018	41	92	15	90	4.7%	2.67 [1.60 , 4.48]
EASI 2017	20	40	14	37	4.7%	1.32 [0.79 , 2.21]
ESCAPE 2015	87	164	43	147	7.9%	1.81 [1.36 , 2.42]
EXTEND-IA 2015	25	35	14	35	5.4%	1.79 [1.13 , 2.82]
IMS III 2013	177	415	86	214	9.5%	1.06 [0.87 , 1.29]
MELT 2007	28	57	22	57	5.8%	1.27 [0.84 , 1.94]
MR CLEAN 2015	76	233	51	267	7.6%	1.71 [1.25 , 2.32]
MR RESCUE 2013	12	64	11	54	2.9%	0.92 [0.44 , 1.92]
PISTE 2016	17	33	12	32	4.3%	1.37 [0.79 , 2.40]
PROACT 2 1999	48	121	15	59	5.0%	1.56 [0.96 , 2.54]
RESILIENT 2020	39	111	22	110	5.4%	1.76 [1.12 , 2.76]
REVASCAT 2015	45	103	29	103	6.4%	1.55 [1.06 , 2.27]
SWIFT PRIME 2015	59	98	33	93	7.4%	1.70 [1.23 , 2.33]
THERAPY 2016	19	50	14	46	4.2%	1.25 [0.71 , 2.19]
THRACE 2016	106	200	85	202	9.3%	1.26 [1.02 , 1.55]
Total (95% CI)		**1997**		**1718**	**100.0%**	**1.54 [1.33 , 1.78]**
Total events:	877		498			

Heterogeneity: Tau² = 0.05; Chi² = 38.51, df = 17 (P = 0.002); I² = 56%
Test for overall effect: Z = 5.85 (P < 0.00001)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. MEDLINE search strategy

The following search strategy was used for MEDLINE (Ovid) and modified for other databases.

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. 1 or 2 or 3
5. radiography, interventional/ or radiology, interventional/
6. catheterization/ or angioplasty/ or angioplasty, balloon/ or angioplasty, balloon, laser-assisted/ or angioplasty, laser/ or atherectomy/ or balloon dilatation/ or catheter ablation/
7. stents/
8. thrombectomy/ or embolectomy/
9. blood vessel prosthesis/ or blood vessel prosthesis implantation/
10. cerebral revascularization/ or reperfusion/ or dilatation/
11. (interventional adj3 (radiolog$ or radiograph$ or neuroradiolog$)).tw.
12. (angioplast$ or stent$).tw.
13. (thrombectomy or thromboaspiration or embolectomy or atherect$).tw.
14. sonothrombolysis.tw.
15. ((mechanical or radiolog$ or pharmacomechanical or laser or endovascular or neurovascular) adj5 (thrombolys$ or reperfusion or fragmentation or aspiration or recanali?ation or clot lys$)).tw.
16. ((clot or thrombus or thrombi or embol$) adj5 (aspirat$ or remov$ or retriev$ or fragmentation or retract$ or extract$ or obliterat$ or dispers$)).tw.
17. ((retrieval or extraction) adj5 device$).tw.
18. endoluminal repair$.tw.
19. (blood vessel adj5 (prosthesis or implantat$)).tw.
20. ((merci or concentric) adj retriever).tw.

21. (endovascular snare$ or neuronet or microsnare or X-ciser or angiojet).tw.
22. or/5-21
23. 4 and 22
24. limit 23 to humans
25. Randomized Controlled Trials as Topic/
26. random allocation/
27. Controlled Clinical Trials as Topic/
28. control groups/
29. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
30. double-blind method/
31. single-blind method/
32. Therapies, Investigational/
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
36. random$.tw.
37. (controlled adj5 (trial$ or stud$)).tw.
38. (clinical$ adj5 trial$).tw.
39. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
40. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
41. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
42. (coin adj5 (flip or flipped or toss$)).tw.
43. or/25-42
44. 24 and 43

Appendix 2. Embase search strategy

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/ or stroke patient/ or stroke unit/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. 1 or 2 or 3
5. interventional radiology/ or endovascular surgery/
6. percutaneous transluminal angioplasty/ or angioplasty/ or laser angioplasty/ or catheterization/ or catheter ablation/ or balloon dilatation/ or exp atherectomy/
7. stent/
8. thrombectomy/ or exp percutaneous thrombectomy/ or embolectomy/
9. artery prosthesis/
10. cerebral revascularization/ or reperfusion/ or artery dilatation/ or recanalization/
11. (interventional adj3 (radiolog$ or radiograph$ or neuroradiolog$)).tw.
12. (angioplast$ or stent$).tw.
13. (thrombectomy or embolectomy or atherect$).tw.
14. thromboaspiration.tw.
15. ((mechanical or radiolog$ or pharmacomechanical or laser or endovascular or neurovascular) adj5 (thrombolys$ or reperfusion or fragmentation or aspiration or recanali?ation or clot lys$)).tw.
16. ((clot or thrombus or thrombi or embol$) adj5 (aspirat$ or remov$ or retriev$ or fragmentation or retract$ or extract$ or obliterat$ or dispers$)).tw.
17. ((retrieval or extraction) adj5 device$).tw.
18. endoluminal repair$.tw.
19. ((blood vessel or artery) adj5 (prosthesis or implantat$)).tw.
20. ((merci or concentric) adj retriever).tw.
21. (endovascular snare$ or neuronet or microsnare or X-ciser or angiojet).tw.
22. ultrasound/ or exp ultrasound therapy/ or echography/ or doppler echography/ or intravascular ultrasound/
23. (ultrasound$ or ultrasonic$ or ultrasonogra$ or sonograph$ or insonation).tw.
24. ((transcranial adj5 doppler) or TCD or TCCD).tw.
25. fibrinolytic therapy/
26. fibrinolytic agent/ or plasmin/ or plasminogen/ or exp plasminogen activator/
27. blood clot lysis/
28. fibrinolysis/

29. (thromboly$ or fibrinoly$ or recanalis$ or recanaliz$ or sonolys$).tw.
30. ((clot$ or thrombus) adj5 (lyse or lysis or dissolve$ or dissolution or fragment$)).tw.
31. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
32. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase).tw.
33. (sonothrombolysis or sonothromboly$ or sonothrombotripsy or thrombotripsy).tw.
34. or/22-33
35. intraarterial drug administration/
36. (intra arterial or intra-arterial or intraarterial or IA).tw.
37. 35 or 36
38. 34 and 37
39. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 38
40. 4 and 39
41. Randomized Controlled Trial/
42. Randomization/
43. Controlled Study/
44. control group/
45. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/
46. Double Blind Procedure/
47. Single Blind Procedure/ or triple blind procedure/
48. random$.tw.
49. (controlled adj5 (trial$ or stud$)).tw.
50. (clinical$ adj5 trial$).tw.
51. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
52. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
53. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
54. (coin adj5 (flip or flipped or toss$)).tw.
55. or/41-54
56. 40 and 55
57. limit 56 to human
58. (carotid or hemorrhag$ or haemorrhag$ or aneurysm$ or fibrillation or trauma$ or aort$ or coronary or myocardial).ti.
59. 57 not 58

Appendix 3. CENTRAL search strategy

IDSearchHits
#1MeSH descriptor: [Cerebrovascular Disorders] this term only1430
#2MeSH descriptor: [Basal Ganglia Diseases] this term only283
#3MeSH descriptor: [Brain Ischemia] explode all trees3575
#4MeSH descriptor: [Carotid Artery Diseases] this term only472
#5MeSH descriptor: [Carotid Artery Thrombosis] this term only18
#6MeSH descriptor: [Carotid Artery Thrombosis] this term only18
#7MeSH descriptor: [Intracranial Arterial Diseases] this term only10
#8MeSH descriptor: [Cerebral Arterial Diseases] this term only26
#9MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees310
#10MeSH descriptor: [Stroke] explode all trees9629
#11(isch?emi* near/6 (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or cva)):ti,ab,kw14611
#12((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) near/5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab,kw16567
#13{or #1-#12}30947
#14MeSH descriptor: [Radiography, Interventional] this term only295
#15MeSH descriptor: [Radiology, Interventional] this term only36
#16MeSH descriptor: [Catheterization] this term only1615
#17MeSH descriptor: [Angioplasty] this term only293
#18MeSH descriptor: [Angioplasty, Balloon] this term only590
#19MeSH descriptor: [Angioplasty, Balloon, Laser-Assisted] this term only26
#20MeSH descriptor: [Angioplasty, Laser] this term only25
#21MeSH descriptor: [Atherectomy] this term only24
#22MeSH descriptor: [Catheter Ablation] this term only1416
#23MeSH descriptor: [Stents] explode all trees4145
#24MeSH descriptor: [Thrombectomy] this term only265
#25MeSH descriptor: [Thrombectomy] this term only265

#26MeSH descriptor: [Blood Vessel Prosthesis] this term only435
#27MeSH descriptor: [Blood Vessel Prosthesis Implantation] this term only447
#28MeSH descriptor: [Cerebral Revascularization] this term only56
#29MeSH descriptor: [Reperfusion] this term only101
#30MeSH descriptor: [Dilatation] this term only425
#31(interventional near/3 (radiolog* or radiograph* or neuroradiolog*)):ti,ab,kw861
#32(angioplast* or stent*):ti,ab,kw20793
#33(thrombectomy or thromboaspiration or embolectomy or atherect*):ti,ab,kw1961
#34(sonothrombolysis):ti,ab,kw101
#35((mechanical or radiolog* or pharmacomechanical or laser or endovascular or neurovascular) near/5 (thrombolys* or reperfusion or fragmentation or aspiration or recanali?ation or clot lys*)):ti,ab,kw783
#36((clot or thrombus or thrombi or embol*) near/5 (aspirat* or remov* or retriev* or fragmentation or retract* or extract* or obliterat* or dispers*)):ti,ab,kw808
#37((retrieval or extraction) near/5 device*):ti,ab,kw131
#38(endoluminal repair*):ti,ab,kw22
#39(blood vessel near/5 (prosthesis or implantat*)):ti,ab,kw833
#40((merci or concentric) near/5 retriever):ti,ab,kw25
#41(endovascular snare* or neuronet or microsnare or X-ciser or angiojet):ti,ab,kw32
#42{or #14-#41}27215
#43#13 and #42 with Cochrane Library publication date Between Sep 2016 and Sep 2020, in Trials1763

Appendix 4. Web of Science search strategy

#1TS=(isch?emi* NEAR/6 (stroke* or apoplex* or “cerebral vasc*” or cerebrovasc* or cva))
#2TS=((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”) NEAR/5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*))
#3#1 or #2
#4TS=(interventional NEAR/3 (radiolog* or radiograph* or neuroradiolog*))
#5TS=(angioplast* or stent*)
#6TS=(thrombectomy or thromboaspiration or embolectomy or atherect*)
#7TS=sonothrombolysis
#8TS=((mechanical or radiolog* or pharmacomechanical or laser or endovascular or neurovascular) NEAR/5 (thrombolys* or reperfusion or fragmentation or aspiration or recanali?ation or clot lys*))
#9TS= ((clot or thrombus or thrombi or embol*) NEAR/5 (aspirat* or remov* or retriev* or fragmentation or retract* or extract* or obliterat* or dispers*))
#10TS=((retrieval or extraction) NEAR/5 device*)
#11TS=”endoluminal repair*”
#12TS=(blood vessel NEAR/5 (prosthesis or implantat*))
#13TS=((merci or concentric) NEAR/5 retriever)
#14TS=(“endovascular snare*” or neuronet or microsnare or X-ciser or angiojet)
#15#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16#3 and #15

Appendix 5. ClinicalTrials.gov search strategy

US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
(thrombectomy OR thromboaspiration OR embolectomy OR endovascular) AND AREA[StudyType] EXPAND[Term] COVER[FullMatch] "Interventional" AND AREA[ConditionSearch] (ischaemic stroke OR brain infarction OR brain ischemia OR carotid artery obstruction OR cerebral ischemia) AND AREA[StudyFirstPostDate] EXPAND[Term] RANGE[09/20/2016, 09/01/2020]
World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch)
Basic search:
1. thrombectomy AND stroke OR thrombectomy AND stroke OR thromboaspiration AND stroke OR embolectomy AND stroke OR endovascular AND stroke
Phases are: ALL
2. thrombectomy AND brain infarction OR thrombectomy AND brain infarction OR thromboaspiration AND brain infarction OR embolectomy AND brain infarction OR endovascular AND brain infarction
Phases are: ALL
3. thrombectomy AND cerebral OR thrombectomy AND cerebral OR thromboaspiration AND cerebral OR embolectomy AND cerebral OR endovascular AND cerebral
Phases are: ALL

WHAT'S NEW

Date	Event	Description
9 August 2021	Amended	Amendments made throughout the review.

HISTORY

Protocol first published: Issue 1, 2009
Review first published: Issue 10, 2010

Date	Event	Description
25 June 2021	Amended	Acknowledgements section amended
15 June 2021	Amended	Title of plain language summary changed
2 December 2020	New citation required and conclusions have changed	The conclusion has changed from the earlier published version, as there is no longer a need for further trials to confirm these results, as was stated in previously published version. The title of the review has changed from 'Percutaneous vascular interventions for acute ischaemic stroke' to 'Endovascular thrombectomy for acute ischaemic stroke'.
1 September 2020	New search has been performed	Review is updated to 1 September 2020 and includes 15 new trials and 3443 new participants. The review now has 19 trials with 3793 participants.

CONTRIBUTIONS OF AUTHORS

All authors drafted the manuscript and approved its content. Eivind Berge passed away in February 2020. Eivind Berge made a substantial contribution to this review before his passing, contributing to the protocol, the design of data extraction sheets, and data extraction. Most of the statistical analysis was done after his passing. All remaining authors deem it highly appropriate and approve that Eivind Berge is listed as author.

DECLARATIONS OF INTEREST

Melinda B Roaldsen:

- Grants and contracts: National Institute for Health Research (NIHR) Cochrane Review Incentive Scheme to be paid on publication of this update. The award will be received by my institution.
- Work as a health professional: "I am a MD and hold a position as a Resident at the Neurological Department in Tromsø, Norway. Currently on leave from clinical work to do research."
- Institution: University Hospital of North Norway, Tromsø, Norway

Mirza Jusufovic: none known
Eivind Berge: none known (deceased)
Haakon Lindekleiv: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Other, Norway

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The name of this review has changed from: 'Percutaneous vascular interventions for acute ischaemic stroke' to: 'Endovascular thrombectomy for acute ischaemic stroke', as that latter is the more common and widespread definition and nomenclature used in both clinical practice and the scientific literature. This change has no implications for the original scope of the review, and is simply a change in terminology.

The previous version of the review included searching of Science Citation Index, ISI Proceedings, LILACS (Latin American and Caribbean Health Sciences Literature database), Google Scholar, ACP Journal Club, DARE (Database of Abstracts of Reviews of Effects), ProQuest Dissertations & Theses, British Library Theses Service, and the National Research Register Archive, as well as handsearching selected journals (*American Journal of Neuroradiology*, *Brain*, *Neuroradiology*, and *Stroke*) (O'Rourke 2010). Based on our experience from the first version of the review, we omitted searches in these sources, as they did not yield additional results and involved considerable efforts.

The previous version of this review included impairment at end of follow-up (e.g. Barthel Index score) as a secondary outcome measure. We did not include this in the updated version because all studies reported functional outcome according to the modified Rankin Scale, and none reported Barthel Index score. Impairment is also covered by the modified Rankin Scale.

In the protocol, we planned to extract time to actual delivery of endovascular thrombectomy therapy. This proved to be very difficult, as most trials reported time to groin puncture or initiation of intra-arterial treatment, therefore we employed the latter in the review.

The subgroup and sensitivity analyses methodology was updated to reflect that these could be performed on specific outcomes. We also included additional subgroups, as the newly included studies identified important subgroups that were not described in our protocol. This is further described in the Methods.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Cause of Death; Fibrinolytic Agents [*administration & dosage]; Infarction, Middle Cerebral Artery [therapy]; Intracranial Hemorrhages [epidemiology] [etiology]; Ischemic Stroke [drug therapy] [*therapy]; Mechanical Thrombolysis [*methods]; Randomized Controlled Trials as Topic; Thrombolytic Therapy [*methods]; Urokinase-Type Plasminogen Activator [administration & dosage]

MeSH check words

Aged; Female; Humans; Male; Middle Aged

Paper III

Roaldsen MB, Lindekleiv H, Mathiesen EB

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

Submitted to *Cochrane Database of Systematic Reviews* June 6, 2021
and re-submitted September 7, 2021

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

Roaldsen MB, Lindekleiv H, Mathiesen EB

Submitted to *Cochrane Database of Systematic Reviews* June 6, 2021
and re-submitted September 7, 2021

TABLE OF CONTENTS

[Intervention Review]

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

Melinda B Roaldsen[1,2], Haakon Lindekleiv[3], Ellisiv B Mathiesen[1,2]

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Contact address: Melinda B Roaldsen, melinda.b.roaldsen@uit.no.

ABSTRACT

Background

About one in five strokes occur during sleep (wake-up stroke). People with wake-up strokes have previously been considered 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, US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). Stroke Trials Registry (last search: 7 December 2017 as 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 of intravenous thrombolytic drugs or endovascular thrombectomy treatments in people with acute ischaemic stroke presenting upon awakening.

Data collection and analysis

Two review authors (MBR and HL) applied the inclusion criteria, extracted data, and assessed trial quality and risk of bias using the GRADE approach. We obtained both published and unpublished data for patients with wake-up strokes. Patients with unknown onset strokes were excluded if the symptoms did not begin on awakening.

Main results

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

For intravenous thrombolytic treatment, good functional outcome (defined as modified Rankin Scale score 0-2) at 90 days follow-up was observed in 66% of participants randomised to thrombolytic treatment and 58% of participants randomised to control (relative risk (RR) 1.13, 95% confidence interval (CI) 1.01 to 1.26, p = 0.03; 763 participants, 5 RCTs; high-certainty evidence). Seven percent 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<0.01; 205 participants, 2 RCTs; high-certainty evidence). Twenty-two percent 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 hemorrhage 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 seven studies were terminated early. More studies are warranted in order to determine the optimal criteria for selecting patients to 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 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 experiment in which people are randomly allocated to one or more treatment groups) up until 24 of May 2021.

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

Key results: This review of seven trials involving a total of 980 participants shows that these treatments can improve functional outcome and survival in selected people with wake-up stroke. It is not possible to rule out that treatment increase the risk of bleeding in the brain. It is still not clear what the optimal selection criteria is when it comes to both imaging criteria and/or time window to choose which patients should receive treatment. These differed between the included trials. More trials to investigate this further is therefore warranted.

Quality of evidence: The available trials were judged to be at low or moderate risk of bias and the overall quality was judged as high certainty evidence.

SUMMARY OF FINDINGS

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

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

Patient or population: Patients 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)	Nr 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: Modified Rankin scale 0-2 at follow-up: 90 days	116 per 1 000	594 per 1 000 (298 to 1 000)	RR 5.12 (2.57 to 10.17)	185 (2 RCTs)	⨁⨁⨁⨁ HIGH**	
Intracranial haemorrhage at follow-up: mean 90 days					-	Data not available from the studies
Death at follow-up: mean 90 days	326 per 1 000	222 per 1 000 (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; **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. 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: Patients 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)	Nr of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard medical care	Risk with Intravenous thrombolytic treatment				
Independent functional outcome at end of follow-up assessed with: Modified Rankin scale 0-2 at follow-up: 90 days	584 per 1 000	660 per 1 000 (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 1 000	19 per 1 000 (5 to 67)	RR 3.47 (0.98 to 12.26)	754 (4 RCTs)	⨁⨁⨁⨁ HIGH	
Death at follow-up: mean 90 days	99 per 1 000	67 per 1 000 (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; **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

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

Other reviews have assessed the benefits of intravenous thrombolytic therapy and intra-arterial stroke therapy (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). A 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 given intravenously are used most commonly and work by dissolving blood clots. These drugs include urokinase, recombinant pro-urokinase (rpro-UK), streptokinase (SK), and recombinant tissue plasminogen activator (rt-PA) including alteplase, duteplase, lumbrokinase, tenecteplase, reteplase, and desmoteplase. Alteplase is the only thrombolytic drug licenced to treat acute ischaemic stroke up to 4.5 hours after symptom onset 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 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 is presenting upon awakening. The optimal selection criteria for treatment have not yet been established. The present review updates a previous version first published in 2014 (Lindekleiv 2014), and updated via Cochrane methods again in 2018 (Roaldsen 2018). After the last update of this review was published, the results of several trials have been completed; four (ECASS-4; EXTEND; THAWS; WAKE-UP) on intravenous thrombolysis and two (DAWN, DEFUSE 3) on endovascular thrombecty and these results could be pooled quantitatively to test 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 on awakening from sleep.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials of intravenous thrombolytic drugs or intra-arterial therapies versus control in people with acute ischaemic stroke presenting upon awakening 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 while awake, we contacted the trial authors to request data for only those participants with wake-up strokes.

Types of interventions

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

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

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

The comparison therapy was standard medical care or placebo.

Types of outcome measures

Primary outcomes

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

Secondary outcomes

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

Search methods for identification of studies

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

Electronic searches

We searched the Cochrane Stroke Group Trials Register (last searched on 24 May 2021) and the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 4 of 12, 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 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;
- contacted manufacturers of relevant devices and equipment (we received a reply from Penumbra Inc.).

Data collection and analysis

Selection of studies

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

Data extraction and management

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

We extracted the following data from each report.

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

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

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

One review author (MBR) entered the data into Review Manager 5.4.1 (RevMan 2020). 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 made direct contact with the relevant principal investigators.

Assessment of risk of bias in included studies

Two review authors (MBR and HL) independently assessed risk of bias for each study. We used the following criteria to assess the quality of reports of eligible trials, according to section 8.5.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the risk of bias according to the following domains.

- Random sequence generation
- Allocation concealment

- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other bias

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

Measures of treatment e9ect

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

Unit of analysis issues

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

Dealing with missing data

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

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis.

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

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

- I^2 of 0% to 30% as no heterogeneity;
- I^2 of 30% to 50% as moderate heterogeneity;
- I^2 of 50% to 80% as substantial heterogeneity;
- I^2 of 80% to 100% as 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 an outcome was assessed in more than 10 studies.

Data synthesis

We used a fixed model for pooled data and considered not pooling data if we encountered considerable heterogeneity (I^2 value 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 have used the GRADEpro GDT to complete the Summary of findings table 1 (GRADEpro GDT 2015).

Subgroup analysis and investigation of heterogeneity

We performed prespecified separate analyses for the primary outcome in the following subgroups where we have been able to obtain data.

- Age (under and over 60 years)
- Sex
- 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 planned on and conducted sensitivity analyses by using the random-effects meta analytic estimate on the primary outcome.

Summary of findings and assessment of the certainty of the evidence

We used GRADE when creating the Summary of findings table. We summarised the 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 unfortunately 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 planned to downgrade the certainty of evidence if deemed necessary using the five GRADE domains (study limitations, imprecision, inconsistency, indirectness, and publication bias) and also in these cases justify all decisions to downgrade the certainty of evidence.

RESULTS

Description of studies

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

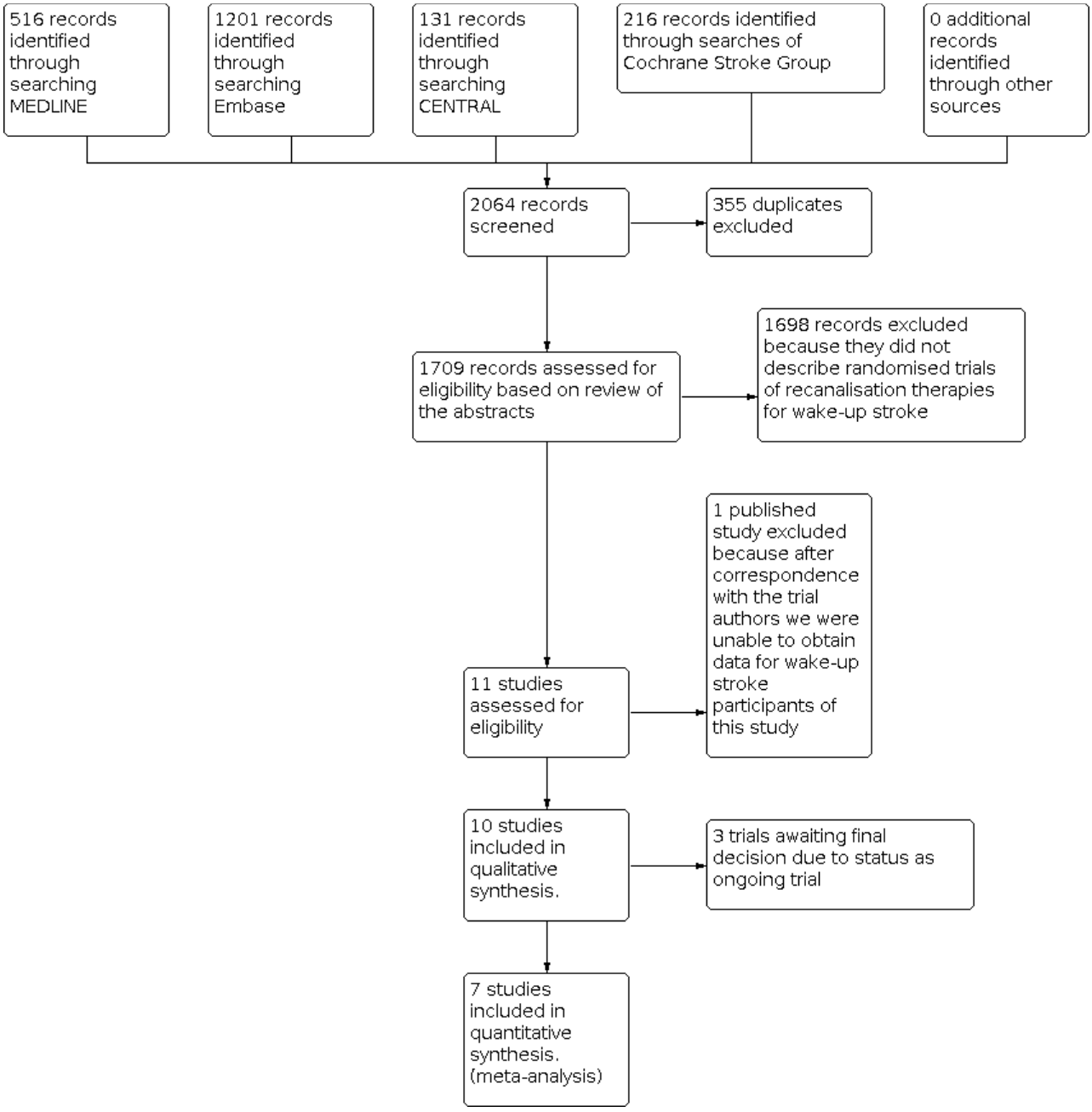
(ECASS-4; EXTEND; Michel 2012; THAWS; WAKE-UP) and two trials examined endovascular thrombectomy versus control (DAWN; DEFUSE 3). All trials included both patients with wake-up strokes and unknown onset strokes. We only included data for patients with wake-up strokes.

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 and excluded 1698 records because the abstract showed that they were not randomised trials of wake-up stroke.

We assessed eleven records in full. We included seven studies. The PRISMA flow diagram is given in Figure 1.

Figure 1. PRISMA flow diagram.



Included studies

The largest trial of all seven included studies was the WAKE-UP trial with 503 participants and whom 449 participants had wake-up stroke and were included in this review. Patients were included in the trial based on findings of magnetic resonance imaging diffusion weighted imaging/fluid attenuated inversion recovery (DWI/FLAIR) mismatch on MRI and randomised to alteplase (0.9 mg/kg) or placebo. THAWS with 131 participants and whom 89 participants

had wake-up stroke were selected by MRI DWI/FLAIR mismatch criteria who were randomised to treatment with alteplase (0.6 mg/kg) or placebo. EXTEND with 225 participants and whom 146 participants had wake-up stroke. Patients were selected by MRI or CT Perfusion core/penumbra mismatch criteria and then randomised to receive alteplase (0.9 mg/kg) or placebo. ECASS-4 had 119 participants of whom 82 participants had wake-up stroke and were included in this review. Patients were selected by MRI Perfusion core/penumbra mismatch criteria and then randomised to receive alteplase (0.9 mg/kg) or placebo. Michel et al conducted a pilot trial that included twelve participants with unknown onset of stroke and of these nine had wake-up stroke and was included in this review. They had signs on perfusion computed tomography of ischaemic tissue at risk of infarction (Michel 2012), all had infarction in the middel cerebral artery territory. Of the nine participants, four were randomised to alteplase (0.9 mg/kg) and five to placebo. DAWN had 206 participants and 114 were wake-up stroke patients. Patients with occlusion of intracranial internal carotid artery or proximal middle cerebral artery last been known to be well 6 to 24 hours were randomised to thrombectomy plus standard care or to standard care alone. DEFUSE 3 had 182 participants and 50% of these were 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

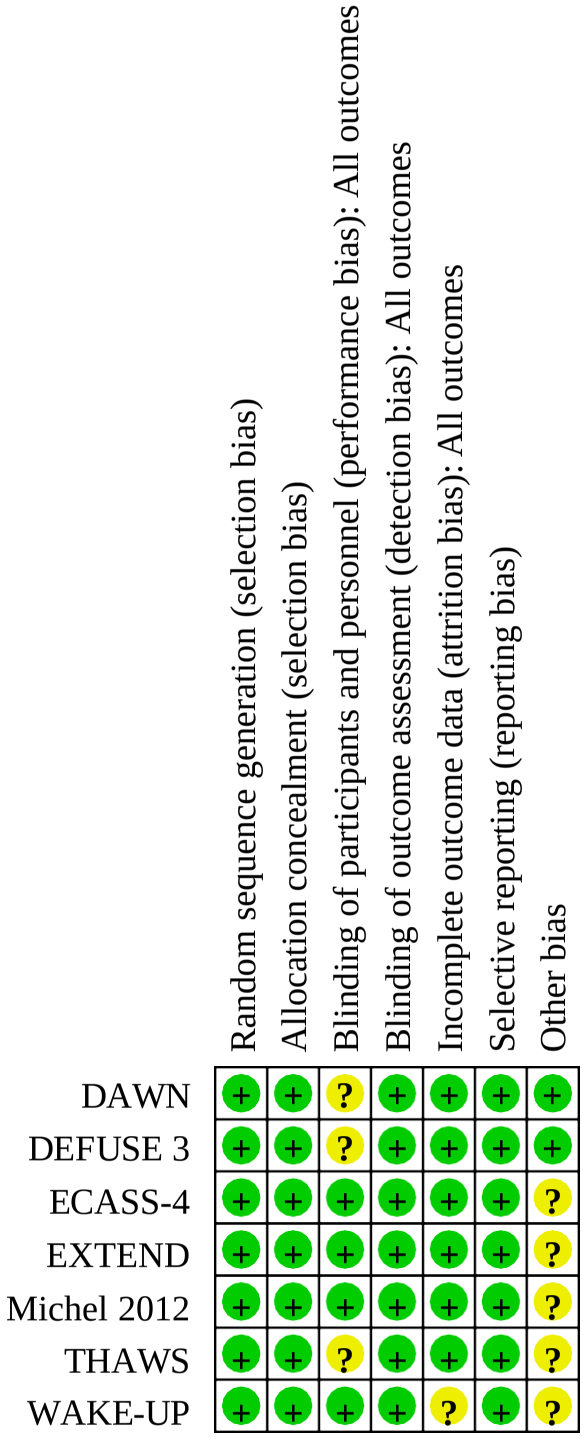
We excluded two studies POSITIVE and NCT01455935. The POSITIVE investigators have not published specific information on wake-up stroke. The contact person of POSITIVE did not respond to our request to share data. NCT01455935 has been put on hold.

We identified two ongoing trials (NCT03181360) and (NCT04256096).

Risk of bias in included studies

See Figure 2.

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



Allocation

The quality of randomisation was adequate in the 7 included studies (DAWN; DEFUSE 3; ECASS-4; EXTEND; Michel 2012; THAWS; WAKE-UP).

Blinding

We assessed 7 studies to be at low risk of bias: (DAWN; DEFUSE 3; ECASS-4; EXTEND; Michel 2012; THAWS; WAKE-UP). The included RCTs of endovascular thrombectomy could not be blinded for investigators or participants due to the nature of the intervention. Three of the included trials (DAWN; DEFUSE 3; THAWS) did not blind the investigators or participants for the allocated treatment. 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 bias to be either unclear or low in all included trials. In: DAWN; ECASS-4; EXTEND; Michel 2012 and THAWS no patients were lost-to follow-up and risk of bias was therefore assessed as low in these trials. In two trials we assessed the risk of bias to be unclear due to the following: in DEFUSE 3 three patients were lost to follow-up and in WAKE-UP thirteen patients were lost to follow-up.

Selective reporting

We assessed 7 studies to be at low risk of bias (DAWN; DEFUSE 3; ECASS-4; EXTEND; Michel 2012; THAWS; WAKE-UP).

Other potential sources of bias

The following six trials were prematurely terminated due to either 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 bias to be unclear.

Effects of interventions

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

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

For intravenous thrombolytic treatment, good functional outcome (defined as modified Rankin Scale score 0-2) at 90 days follow-up was observed in 66% of participants randomised to thrombolytic treatment and 58% of participants randomised to control, relative risk (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)

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<0.01; 205 participants, 2 RCTs; high-certainty evidence).(Analysis 1.1)

Death at the end of 90 days follow-up

Data were available for 763 participants for treatment with intravenous thrombolytic treatment. Seven percent 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) Twenty-two percent of participants randomised to endovascular thrombectomy and 33% of participants randomised to control had died at 90 days follow up (95% CI 0.43 to 1.07, p=0.10; 205 participants, 2 RCTs, high-certainty evidence). (Analysis 2.1).

Symptomatic intracranial haemorrhage at the end of follow-up

Data were available from four studies of intravenous thrombolytic treatment for ischaemic wake-up stroke of 754 patients (ECASS-4; EXTEND; THAWS; WAKE-UP). Symptomatic intracranial haemorrhage occured 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).

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 (ECASS-4; EXTEND; THAWS; WAKE-UP), (RR 1.08, 95% CI 0.93 to 1.25) versus (RR 1.15, 95% CI 1.01 to 1.32). The cutoff for younger and older patients 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 (ECASS-4; EXTEND; THAWS; WAKE-UP) (RR 1.07, 95% CI 0.89 to 1.30) versus (RR 1.11, 95% CI 0.96 to 1.29) (Analysis 4.2).

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, (EXTEND; THAWS; WAKE-UP) (RR 1.31, 95% CI 0.93 to 1.85) versus (RR 1.12, 95% CI 1.01 to 1.24) (Analysis 4.4).

Time from first observation of symptoms to onset of treatment

There was similar effect of thrombolytic treatment on functional outcome in participants treated within 3 hours after awakening and >3 hours after awakening from three trials that provided subgroup data on time from first observation of symptoms to onset

of treatment (ECASS-4; THAWS; WAKE-UP) (RR 1.06, 95% CI 0.90 to 1.24) versus (RR 1.12, 95% CI 0.96 to 1.32) (Analysis 4.5).

Sensitivity analyses

The sensitivity analysis using a random-effects model (Analysis 5.1; Analysis 5.2) found similar results compared to the fixed-effects 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 (risk ratio 5.12, 95% CI 2.57 to 10.1) in selected patients with wake-up stroke and large vessel occlusion in the anterior circulation treated in the 6-24 hour time window. The effect estimate for patients 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 patients (of whom 91 with 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 patients (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 6-24 h window than in the higher. 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 patients. In WAKE-UP 53% of patients in the alteplase group and 42% in the placebo group achieved a favourable outcome, defined as modified Rankin Scale 0-1; a difference in treatment effect which is comparable to that seen in patients treated within 3 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 patients 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 and that this is a potential source of bias. WAKE-UP was terminated early because of lack of funding and ECASS-4 because of slow enrolment. EXTEND and THAWS were prematurely terminated after the publication of the results from WAKE-UP. Thus, results must 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 included in the present 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 CTP penumbra for selection of patients. 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 (WAKE-UP). 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

Participants from the included studies may not be representative of all patients with ischaemic wake-up stroke. There is high evidence that intravenous thrombolytic treatment improves functional and neurological outcomes without increasing death in selected patients with wake-up stroke and there is high 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 (risk ratio 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 6-24 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 to1.26).

Quality of the evidence

We prepared "Summary of findings" tables using GRADEpro and Cochrane methods.

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

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 (DAWN; DEFUSE 3; THAWS) of the included trials were not blinded for allocated treatment. 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 trials included in the present review included interim analyses showing efficacy (DAWN; DEFUSE 3), lack of equipoise or slow recruitment (ECASS-4; EXTEND; THAWS), or lack of funding (WAKE-UP).

Potential biases in the review process

The strengths 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 included studies performed follow-up at the same time interval, 90 days. This systematic review also

has some limitations. A limited number of studies was available for inclusion and the number of participants was rather low. Potential biases in the review process were minimized 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 risk of the bias assessment. The findings and the conclusions in this review are affected by the quality, quantity, and outcome reporting of all the included trials.

Agreements and disagreements with other studies or reviews

We have identified some systematic reviews and meta-analysis on thrombolytic treatment for ischaemic wake-up stroke. Buck and coworkers (Buck 2014) did a systematic review of eleven studies (one RCT, three case reports/series and seven observational studies) but did not perform any statistical analysis because of considerable heterogeneity of reported methods and data. A meta-analysis of individual patient data from ECASS-4, EXTEND, THAWS, and WAKE-UP (Thomalla 2020) found a stronger effect estimate for the primary outcome mRS 0-1 than we did for the primary outcome of mRS 0-2 in the present study. A recently published comprehensive review and meta-analysis on thrombolytic treatment for wake-up stroke included two RCTs (WAKE-UP; THAWS) five comparative cohort studies and nine non-comparative single group studies (Mac Grory 2021). We have not been able 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 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 and also further explore whether a larger proportion of wake-up stroke patients can safely receive an effective acute treatment.

All the trials included in the 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 all 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 protocol (Task Force of the Working Group 1994).

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CHARACTERISTICS OF STUDIES

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

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DAWN

Study characteristics	
Methods	International, multicentre, prospective, randomised, open-label trial with blinded assessment of end-points
Participants	Participants 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. They must have clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke, and subject belongs to one of the following subgroups: Subject has failed IV t-PA therapy (defined as a confirmed persistent occlusion 60 min after administration). Subject is contraindicated for IV t-PA administration. Age ≥18 Baseline NIHSS ≥10 (assessed within one hour prior to measuring core infarct volume) Subject can be randomized between with 6 to 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 end-point was mean score of mRS at 90 days.
Notes	Funding source: Stryker Neurovascular. Prematurely terminated 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 for the two treatment groups and was stratified according to mismatch criteria, the interval between the time that the patient 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 end-points
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up
Selective reporting (reporting bias)	Low risk	No patient lost to follow-up and provided intention-to-treat analysis.

DAWN *(Continued)*

Other bias	Low risk	At 31 months and 206 patients enrolled the trial was stopped because of the results of a prespecified interim analysis. Adaptive trial design with sample size from 150 to 500 patients.

DEFUSE 3

Study characteristics	
Methods	Multicenter, randomised, open-label trial with blinded outcome assessment
Participants	Patients with acute ischaemic stroke presenting between 6-16 hours from last known well and with remaining brain tissue that was not yet infarcted. Patients with proximal middle-cerebral-artery or internal-carotid-artery occlusion, an initial infarct size of less than 70 ml, and a ratio of the volume of the ischemic tissue on perfusion imaging to infarct volume of 1.8 or more
Interventions	Endovascular thrombectomy plus standard medical treatment vs. standard medical treatment alone
Outcomes	Primary outcome was the ordinal score on the modified Rankin scale at day 90 follow-up Secondary outcomes was functional independance mRS 0-2 at day 90. Primary safety outcome was death within 90 days and the occurence 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 sympton onset to enrollment, 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 sympton onset to enrollment, 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 end-point assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 patients lost to follow-up and provided intention to treat analysis
Selective reporting (reporting bias)	Low risk	Provided intention to treat analysis
Other bias	Low risk	After an early interim analysis after the DAWN trial results and after 182 randomised patient 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.
Participants	Patients with acute ischaemic stroke if treatment could be started within 4.5-9 hours after symptom onset. Wake-up stroke could be included if they fulfilled the other criteria. 119 participanst whom 63 had wake-up stroke. The study authors contributed unpublished data on the participants with wake-up stroke.
Interventions	Patients were randomised to either intravenous thrombolysis with rt-PA, alteplase (0.9 mg/kg) or placebo
Outcomes	Primary end-point was categorical shift in the mRS at day 90. Secondary endpoints were favorable outcome mRS 0-1 versus unfavorable outcome 2-6, improvement of neurological status measured by NIHSS, reperfusion at 12-24 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	None 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 participants of 264 planned participants.

EXTEND

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled trial

EXTEND *(Continued)*

Participants	225 participants whom 146 had wake-up stroke. The study authors contributed unpublished data on the participants with wake-up stroke. Inclusion criteria • Participants presenting with acute ischaemic stroke • Participant, family member or legally responsible person depending on local ethics requirements has given informed consent • Participant's age is ≥ 18 years • Treatment onset can commence within ≥ 3 to 9 hours after stroke onset according to registered product information, or within 4.5 to 9 hours according to locally accepted guidelines.* (*Guidelines are currently under international review - advisory statement issued by the Stroke Council, American Heart Association, and American Stroke Association.) • Patients who awake with stroke may be included if neurological and other exclusion criteria are satisfied. These 'wake-up' strokes are defined as having no symptoms at sleep onset, but stroke symptoms on waking. The time of stroke onset is to be taken as the midpoint between sleep onset (or last known to be normal) and time of waking. The maximum time window for randomisation is then 9 hours from the midpoint as described • NIHSS score of ≥ 4 to 26 with clinical signs of hemispheric infarction • Penumbral imaging - using a Tmax > 6-second delay, a perfusion (PWI) lesion volume to diffusion (DWI) lesion volume ratio > 1.2, a DWI volume ≤ 70 mL, and a perfusion lesion volume-diffusion lesion volume difference > 10 mL • Patients may be consented before or after penumbral screening depending upon local practice. The entire cohort of patients consented into the study will be followed up with clinical assessments and biomarker studies regardless of eligibility for randomisation to treatment based on penumbral mismatch criteria Exclusion criteria • Intracranial haemorrhage identified by CT or MRI • Rapidly improving symptoms, particularly if in the judgement of the managing clinician improvement is likely to result in the patient having an NIHSS score of < 4 at randomisation • Pre-stroke mRS score of ≥ 2 (indicating previous disability) • Contraindication to imaging with magnetic resonance with contrast agents • Infarct core > 1/3 middle cerebral artery territory qualitatively • Participation in any investigational study in the previous 30 days • Any terminal illness such that the patient would not be expected to survive more than 1 year • Any condition that could impose hazards to the patient if study therapy is initiated or affect the participation of the patient in the study (this applies to patients with severe microangiopathy such as haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura). The judgement is leC to the discretion of the investigator • Pregnant women (clinically evident) • Previous stroke within last 3 months • Recent past history or clinical presentation of intracerebral haemorrhage, subarachnoid haemorrhage, arteriovenous malformation, aneurysm, or cerebral neoplasm. At the discretion of each investigator • Current use of oral anticoagulants and a prolonged prothrombin time (INR > 1.6) • Use of heparin, except for low-dose subcutaneous heparin, in the previous 48 hours and an activated prolonged partial thromboplastin time exceeding the upper limit of the local laboratory normal range • Use of glycoprotein IIb-IIIa inhibitors within the past 72 hours. Use of single or dual agent oral platelet inhibitors (clopidogrel and/or low-dose aspirin) prior to study entry is permitted • Clinically significant hypoglycaemia • Uncontrolled hypertension defined by a blood pressure > 185 mmHg systolic or > 110 mmHg diastolic on at least 2 separate occasions at least 10 minutes apart, or requiring aggressive treatment to reduce the blood pressure to within these limits. The definition of 'aggressive treatment' is left to the discretion of the responsible investigator • Hereditary or acquired haemorrhagic diathesis

EXTEND *(Continued)*

	• Gastrointestinal or urinary bleeding within the preceding 21 days • Major surgery within the preceding 14 days that poses risk in the opinion of the investigator • Exposure to a thrombolytic agent within the previous 72 hours
Interventions	• Intravenous tissue plasminogen activator (alteplase) 0.9 mg/kg body weight up to a maximum of 90 mg, 10% as bolus, 90% over 1 hour as infusion • Matching placebo
Outcomes	mRS 0 to 1 at 90 days' follow-up
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 the 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	None lost to follow-up
Selective reporting (reporting bias)	Low risk	Intention-to treat analysis was provided.
Other bias	Unclear risk	Prematurely terminated 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 middle cerebral artery territory and significant volume of at-risk tissue on perfusion computed tomography. 9 of the participants had wake-up stroke, and 3 had a non-wake-up stroke of unknown onset. The study authors contributed unpublished data on the 9 participants with wake-up stroke.

Michel 2012 *(Continued)*

Interventions	• Intravenous tissue plasminogen activator (alteplase) 0.9 mg/kg body weight up to a maximum of 90 mg, 10% as bolus, 90% over 1 hour as infusion • Matching placebo
Outcomes	Primary outcome: feasibility of study Secondary outcome: mRS 0 to 2 at 90 days' follow-up
Notes	Principal Investigator: Patrik Michel, University of Lausanne, Lausanne, Switzerland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table generated by independent pharmacist
Allocation concealment (selection bias)	Low risk	Enrolment of participants and allocation performed by blinded physician.
Blinding of participants and personnel (performance bias) 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	None loss 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 whom 89 had wake-stroke. The study authors contributed unpublished data on the 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. awakening) • Acute stroke MRI including DWI and FLAIR completed • ASPECTS on initial DWI is 5 or more • No marked parenchymal hyperintensity visible on FLAIR

THAWS *(Continued)*

- Initial NIHSS ≥ 5 and ≤ 25
- Written informed consent by patient or next of kin

Exclusion criteria

- Pre-stroke mRS > 1 (patients who have inability to carry out all daily activities and require some help or supervision)
- Contraindications in the Japanese guideline for the intravenous application of recombinant tissue-type plasminogen activator (alteplase)
- History of non-traumatic intracranial haemorrhage
- History of stroke within the last 1 month (excluding transient ischaemic attack)
- History of significant head/spinal injury or surgery within the last 3 months
- History of gastrointestinal or urinary tract bleeding within the last 21 days
- History of major surgery or significant trauma other than head injury within the last 14 days
- Hypersensitivity to alteplase
- Suspected subarachnoid haemorrhage
- Concurrent acute aortic dissection
- Concurrent haemorrhage (e.g. intracranial, gastrointestinal, urinary tract, or retroperitoneal, haemoptysis)
- Systolic blood pressure ≥ 185 mmHg despite antihypertensive therapy
- Diastolic blood pressure ≥ 110 mmHg despite antihypertensive therapy
- Significant hepatic disorder
- Acute pancreatitis
- Blood glucose < 50 mg/dL or > 400 mg/dL
- Platelet count ≤ 100,000/mm^3
- International normalised ratio of prothrombin time > 1.7 or prolonged aPTT > 1.5 times the baseline value (> approximately 40 seconds only as a guide) for patients on anticoagulation therapy or those with abnormal coagulation
- Any contraindication to MRI (e.g. cardiac pacemaker)
- Extensive early ischaemic change in brainstem or cerebellum (e.g. more than half of brainstem or more than 1 hemisphere of cerebellum)
- Planned or anticipated treatment with surgery or endovascular reperfusion strategies (e.g. intra-arterial thrombolysis, mechanical recanalisation techniques)
- Pregnant, lactating, or potentially pregnant
- Life expectancy 6 months or less by judgement of the investigator
- Inappropriate for study enrolment by judgement of the investigator

Interventions	• Intravenous tissue plasminogen activator (alteplase) 0.6 mg/kg body weight up to a maximum of 60 mg, 10% as bolus, 90% over 1 hour as infusion • Best medical care
Outcomes	Favourable outcome (mRS score 0 to 1) at 90 days' follow-up
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 the 300 planned participants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated

THAWS *(Continued)*

Allocation concealment (selection bias)	Low risk	Web-based randomisation
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	None lost to follow-up
Selective reporting (reporting bias)	Low risk	Intention to treat analysis was provided
Other bias	Unclear risk	Prematurely terminated 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 whom 449 had wake-up stroke. The study authors contributed unpublished data on the participants with wake-up stroke. Clinical inclusion criteria • Clinical diagnosis of acute ischaemic stroke with unknown symptom onset (e.g. stroke symptoms recognised on awakening) • Last known well (without neurological symptoms) > 4.5 hours of treatment initiation • Measurable disabling neurological deficit (defined as an impairment of 1 or more of the following: language, motor function, cognition, gaze, vision, neglect) • Age 18 to 80 years • Treatment can be started within 4.5 hours of symptom recognition (e.g. awakening) • 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

WAKE-UP *(Continued)*

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

Imaging exclusion criteria

- Poor MRI quality precluding interpretation according to the study protocol
- Any sign of intracranial haemorrhage on baseline MRI
- FLAIR showing a marked parenchymal hyperintensity in a region corresponding to the acute DWI lesion indicative of an acute ischaemic lesion with a high likelihood of being > 4.5 hours old
- Large DWI lesion volume > 1/3 of the middle cerebral artery or > 50% of the anterior cerebral artery or posterior cerebral artery territory (visual inspection) or > 100 mL
- Any MRI findings indicative of a high risk of symptomatic intracranial haemorrhage related to potential IV alteplase treatment in the judgement of the investigator

Interventions	• IV tissue plasminogen activator (alteplase) 0.9 mg/kg body weight up to a maximum of 90 mg, 10% as bolus, 90% over 1 hour as infusion • Matching placebo
Outcomes	• Favourable outcome (mRS 0 to 1) at 90 days' follow-up • Mortality at 90 days' follow-up • Death or dependency (mRS 4 to 6) at 90 days' follow-up

WAKE-UP *(Continued)*

Notes	ClinicalTrials.gov identifier: NCT01525290. Funding Source: Supported by a grant (278276) from the European Union Seventh Framework Program. Trial was terminated after 503 participants of estimated and planned 800 target sample size due to 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 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 estimated and planned 800 target sample size due to financial reasons.

mRS: modified Rankin Scale

Characteristics of studies awaiting classification *[ordered by study ID]*

POSITIVE

Methods	Randomised, single-blinded trial
Participants	750 participants Inclusion criteria • Age 18 and older (i.e. candidates must have had their 18th birthday) • NIHSS ≥ 8 at the time of neuroimaging • Presenting or persistent symptoms within 6 to 12 hours of when groin puncture can be obtained • Neuroimaging demonstrates large vessel proximal occlusion (distal internal carotid artery through middle cerebral artery M1 bifurcation) • The operator feels that the stroke can be appropriately treated with traditional endovascular techniques (endovascular mechanical thrombectomy without adjunctive devices such as stents) • Patients within 6 to 12 hours of symptom onset who have received intravenous alteplase without improvement in symptoms are eligible for this study. Patients presenting earlier than 6 hours should be treated according to local standard of care • Pre-event mRS score 0 to 1 • Consenting requirements met according to local institutional review board

POSITIVE *(Continued)*

	Exclusion criteria • Patient is less than 6 hours from symptom onset • Rapidly improving neurologic examination • Absence of large vessel occlusion on non-invasive imaging • Known or suspected pre-existing (chronic) large vessel occlusion in the symptomatic territory • Absence of an associated large penumbra as defined by physiologic imaging according to standard of practice at the participating institution • Any intracranial haemorrhage in the last 90 days • Known irreversible bleeding disorder • Known hereditary or acquired haemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR > 2.5 or institutionally equivalent prothrombin time of 2.5 times normal • Platelet count < 100 x 103 cells/mm^3 or known platelet dysfunction • Inability to tolerate, clinically documented evidence in medical history of adverse reaction, or contraindication to medications used in treatment of the stroke • Contraindication to CT or MRI (i.e. iodine contrast allergy or other condition that prohibits imaging from either CT or MRI) • Known allergy to contrast used in angiography that cannot be medically controlled • Relative contraindication to angiography (e.g. serum creatinine > 2.5 mg/dL) • Women who are currently pregnant or breastfeeding (women of childbearing potential must have a negative pregnancy test prior to the study procedure - either serum or urine) • Evidence of active infection (indicated by fever at or over 99.9 °F and/or open draining wound) at the time of randomisation • Current use of cocaine or other vasoactive substance • Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments through 90 days • Patients who lack the necessary mental capacity to participate or who are unwilling or unable to comply with the protocol's follow-up appointment schedule (based on the investigator's judgement) Head CT or MRI scan exclusion criteria • Presence of blood on imaging (subarachnoid haemorrhage, intracerebral haemorrhage, etc.) • High-density lesion consistent with haemorrhage of any degree • Significant mass effect with midline shift • Large (more than 1/3 of the middle cerebral artery) regions of clear hypodensity on the baseline CT scan or ASPECTS of < 7; sulcal effacement and/or loss of grey-white differentiation alone are not contraindications for treatment
Interventions	Endovascular treatment plus best medical treatment or best medical treatment alone
Outcomes	mRS score at 90 days' follow-up
Notes	ClinicalTrials.gov identifier: NCT01852201 Not a trial of wake-up stroke per se, but the trial will include a substantial proportion of participants with wake-up stroke.

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

NCT01455935

Study name	WAke up Symptomatic Stroke in Acute Brain Ischemia (WASSABI) trial

NCT01455935 *(Continued)*

Methods	Randomised, single-blinded, controlled trial
Participants	90 participants Inclusion criteria • Age: 18 to 80 years old • Ischaemic wake-up stroke (unknown time of onset but < 24 hours since last seen normal) • NIHSS 8 to 22 • Evidence of penumbra on CT perfusion as mentioned above • ASPECTS 7 or more • Signed informed consent Exclusion criteria • Evidence of intracranial haemorrhage (intracerebral haematoma, intraventricular haemorrhage, subarachnoid haemorrhage, epidural haemorrhage, acute or chronic subdural haematoma) on the baseline CT • Historical mRS of ≥ 2 • NIHSS < 8 at the time of treatment • Positive pregnancy test in women at age of childbearing • Intracranial or intraspinal surgery within 3 months • Stroke or serious head injury within 3 months • History of intracranial haemorrhage • Uncontrolled hypertension at time of treatment (e.g. > 185 mmHg systolic or > 110 mmHg diastolic) • Seizure at the onset of stroke • Active internal bleeding • Intracranial neoplasm • Arteriovenous malformation or aneurysm • Clinical presentation suggesting post-myocardial infarction pericarditis • Known bleeding diathesis including but not limited to current use of oral anticoagulants producing an INR > 1.7 • INR > 1.7 • Administration of heparin within 48 hours preceding the onset of stroke with an elevated aPTT at presentation • Platelet count < 100,000/mm^3 • Major surgery within 2 weeks • Gastrointestinal or urinary tract haemorrhage within 3 weeks • Aggressive treatment required to lower blood pressure • Glucose level < 50 or > 400 mg/dL • Arterial puncture at a non-compressible site or lumbar puncture within 1 week
Interventions	• Best medical care • Intravenous tissue plasminogen activator (alteplase) 0.9 mg/kg body weight up to a maximum of 90 mg, 10% as bolus, 90% over 1 hour as infusion • Intra-arterial therapy (choice of intra-arterial therapy by endovascular surgeon)
Outcomes	mRS at 90 days' follow-up
Starting date	November 2011
Contact information	Principal Investigator: Tareq Kass-Hout, Jacobs Neurological Institute, University at Buffalo Neurosurgery, USA

NCT01455935 *(Continued)*	
	E-mail: kasshouttareq@gmail.com
Notes	ClinicalTrials.gov identifier: NCT01455935

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: • Infarction comprising more than > 1/3 of the middle cerebral artery territory on plain CT or CT perfusion • Intracranial haemorrhage, structural brain lesions that can mimic stroke (e.g. cerebral tumour) • 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) • 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

NCT03181360 *(Continued)*	• 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 0-1 • Good functional outcome: mRS 0-2 • 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 an 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 • Re-hospitalisations 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.

NCT04256096	
Study name	Randomization of Endovascular Treatment in Acute Ischemic Stroke in the Extended Time Window (RESILIENTExt)
Methods	A phase III, randomized, multi-center, 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 ischemic stroke within 8-24 hours from time last seen well
Participants	1. Acute ischemic stroke where patient is ineligible for IV thrombolytic treatment or the treatment is contraindicated (e.g., subject presents beyond recommended time from symptom onset), or where patient has received IV thrombolytic therapy without clinical improvement. 2. No significant pre-stroke functional disability (mRS ≤2) 3. Baseline NIHSS score obtained prior to randomization must be equal or higher than 8 points (assessed within one hour prior to qualifying imaging) 4. Age ≥18 years (no upper age limit) 5. Occlusion (TICI 0-1) 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. 6. Patient treatable within 6-24 hours of symptom onset. Symptoms onset is defined as point in time the patient was last seen well (at baseline). Treatment start is defined as arterial puncture. 7. Informed consent obtained from patient or acceptable patient surrogate 8. Estimated enrollment is 376 participants
Interventions	Endovascular treatment of large vessel occlusion (mechanical thrombectomy) with stent-retriever and/or thromboaspiration (neurointerventionalist choice)
Outcomes	Distribution of the modified Rankin Scale scores at 90 days (shift analysis). The score range from zero to 6 with higher values indicating a worst functional outcome at 90 days
Starting date	March 9, 2020
Contact information	Sheila CO Martins, MD, PhD
Notes	ClinicalTrials.gov Identifier: NCT04256096

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

DATA AND ANALYSES

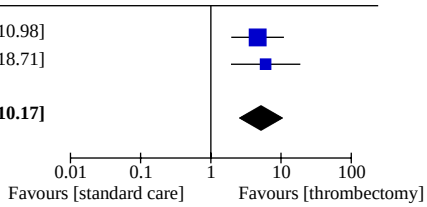
Comparison 1. Good functional outcome (modified Rankin scale score 0-2) at 90 days follow-up

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 0-2) 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			

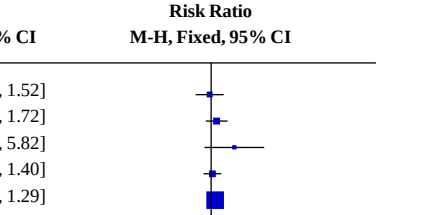
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 4.66 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Good functional outcome (modified Rankin scale score 0-2) 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



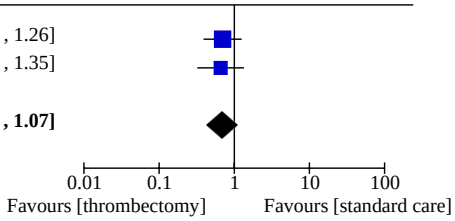
Comparison 2. Death at 90 days follow-up

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]

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

Study or Subgroup	Endovascular Events	Total	Control Events	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			

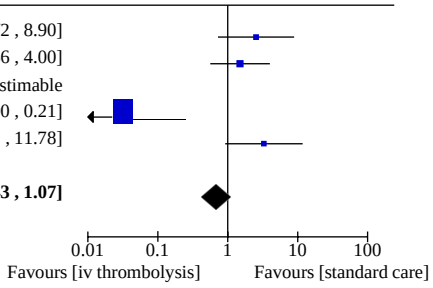
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable



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

Study or Subgroup	Intravenous thrombolysis Events	Total	Control Events	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



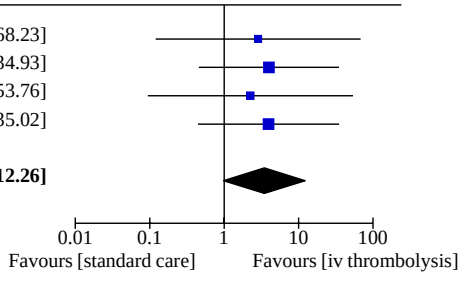
Comparison 3. Symptomatic intracranial haemorrhage

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	Total	Control Events	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

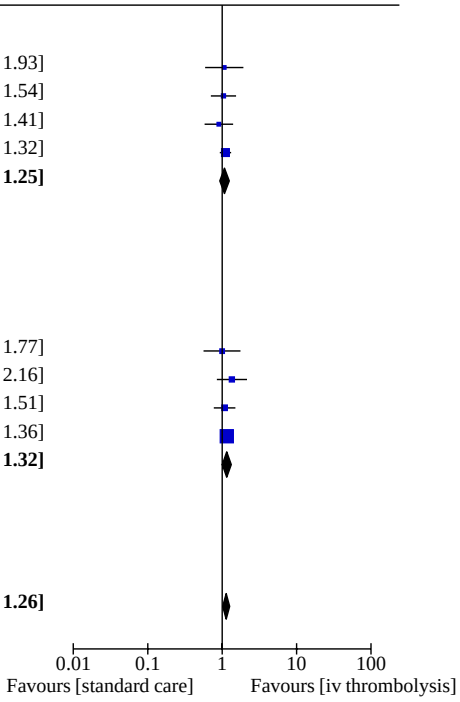


Comparison 4. Subgroup analyses for good functional outcome after intravenous thrombolytic treatment

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]

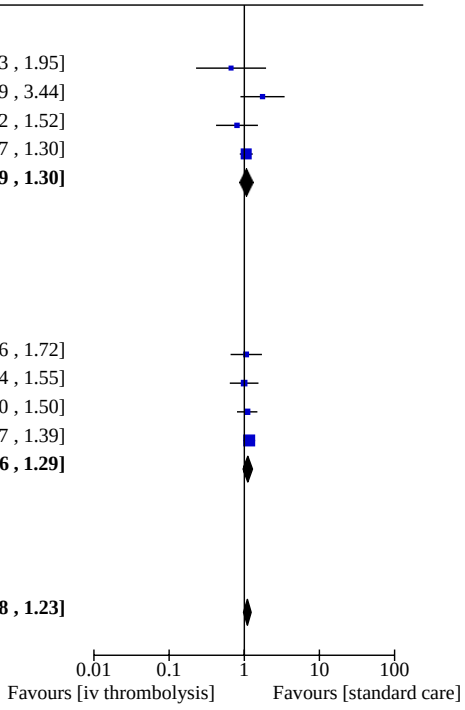
Analysis 4.1. Comparison 4: Subgroup analyses for good functional outcome after intravenous thrombolytic treatment, Outcome 1: Age

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%						



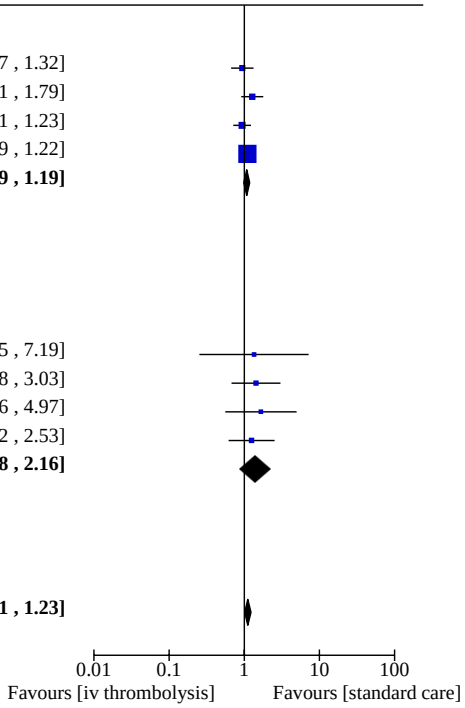
Analysis 4.2. Comparison 4: Subgroup analyses for good functional outcome after intravenous thrombolytic treatment, Outcome 2: Sex

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%						



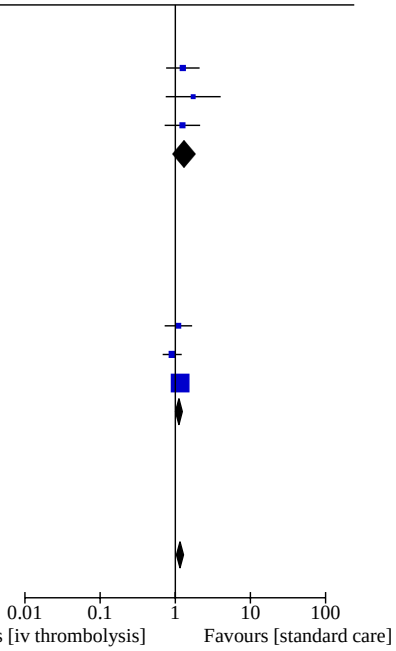
Analysis 4.3. Comparison 4: Subgroup analyses for good functional outcome after intravenous thrombolytic treatment, Outcome 3: NIHSS score

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%						



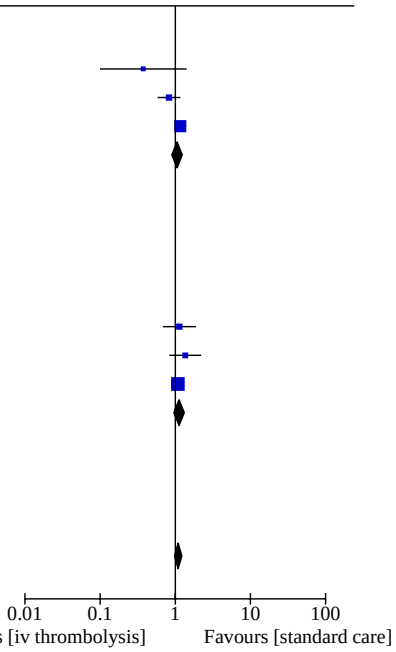
Analysis 4.4. Comparison 4: Subgroup analyses for good functional outcome after intravenous thrombolytic treatment, Outcome 4: Findings on imaging

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%						



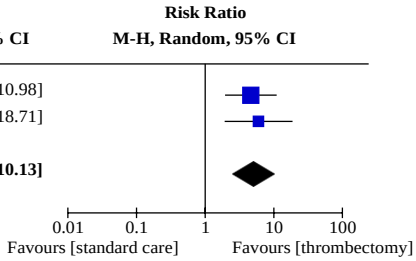
Comparison 5. Sensitivity analysis

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)

Study or Subgroup	Endovascular treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
DAWN	33	67	5	47	63.4%	4.63 [1.95 , 10.98]
DEFUSE 3	21	49	3	42	36.6%	6.00 [1.92 , 18.71]
Total (95% CI)		**116**		**89**	**100.0%**	**5.09 [2.56 , 10.13]**
Total events:	54		8			

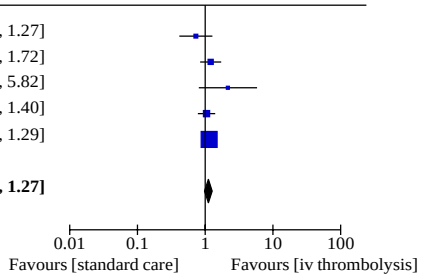
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 4.64 (P < 0.00001)
Test for subgroup differences: Not applicable



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

Study or Subgroup	Intravenous thrombolysis Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ECASS-4	12	32	16	31	5.1%	0.73 [0.41 , 1.27]
EXTEND	36	73	30	73	11.9%	1.20 [0.84 , 1.72]
Michel 2012	4	4	2	5	1.7%	2.16 [0.80 , 5.82]
THAWS	35	51	25	38	17.1%	1.04 [0.78 , 1.40]
WAKE-UP	164	220	142	217	64.2%	1.14 [1.01 , 1.29]
Total (95% CI)		**380**		**364**	**100.0%**	**1.12 [0.98 , 1.27]**
Total events:	251		215			

Heterogeneity: Tau² = 0.00; Chi² = 4.41, df = 4 (P = 0.35); I² = 9%
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



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

#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

#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.

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 insuEiciency/ 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.

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

Keywords: wake

Appendix 7. ISRCTN Registry search strategy

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

WHAT'S NEW

Date	Event	Description
2 June 2021	New search has been performed	Title 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 search has been performed	This review has been updated with searches performed on 24 of May 2021 and now includes 6 new trials with a total of 7 trials with 980 participants.
7 April 2021	New citation required and conclusions have changed	Conclusion has been updated and changed from earlier published version.

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.

DECLARATIONS OF INTEREST

MBR: *Financial interest: Other:* International Trial Manager for TWIST (Tenecteplase in Wake-up Ischaemic Stroke Trial), University Hospital of North Norway NCT03181360 A protocol article about rationale for and design of TWIST has been published in International Stroke Journal. NCT03181360
HL: Co-drafted the protocol for NCT03181360
EBM: *Non-financial/other interests:* Co-ordinating Investigator of the Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST), University Hospital of North Norway, Tromso, Norway: A protocol article about rationale for and design of TWIST has been published in International Stroke Journal. NCT03181360

SOURCES OF SUPPORT

Internal sources

- No sources of support provided, Other

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We unfortunately have not been able to procure data on 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 have split the statistical analysis for studies where patients receive intravenous thrombolysis and for the studies where patients receive endovascular thrombectomy. This was done after confering with and with the advice received from the Cochrane Stroke Group.

This review has been renamed 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.

Paper IV

Roaldsen MB, Lindekleiv H, Eltoft A, Jusufovic M, Søyland M-H, Petersson J, Indredavik B, Tveiten A, Putaala J, Christensen H, Kõrv J, Jatuzis D, Engelter ST, de Marchis GM, Wilsgaard T, Werring DJ, Robinson T, Mathiesen EB, Berge E

Tenecteplase in wake-up ischaemic stroke trial (TWIST): Protocol for a randomised controlled trial

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Tenecteplase in wake-up ischemic stroke trial: Protocol for a randomized-controlled trial

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Abstract

Background: Patients with wake-up ischemic stroke who have evidence of salvageable tissue on advanced imaging can benefit from intravenous thrombolysis. It is not known whether patients who do not fulfil such imaging criteria might benefit from treatment, but studies indicate that treatment based on non-contrast CT criteria may be safe. Tenecteplase has shown promising results in patients with acute ischemic stroke. The aim of the Tenecteplase in Wake-up Ischemic Stroke Trial (TWIST) is to compare the effect of thrombolytic treatment with tenecteplase and standard care versus standard care alone in patients with wake-up ischemic stroke selected by non-contrast CT.

Methods/design: TWIST is an international, investigator-initiated, multi-centre, prospective, randomized-controlled, open-label, blinded end-point trial of tenecteplase ($n = 300$) versus standard care ($n = 300$) in patients who wake up with an acute ischemic stroke and can be treated within 4.5 h upon awakening. Seventy-seven centres in 10 countries (Denmark, Estonia, Finland, Latvia, Lithuania, New Zealand, Norway, Sweden, Switzerland, and the United Kingdom) participate. The primary outcome is the modified Rankin Scale on the ordinal scale (0–6) at three months.

Discussion: TWIST aims to determine the effect and safety of thrombolytic treatment with tenecteplase in patients with wake-up ischemic stroke selected by non-contrast CT.

Trial registration: ClinicalTrials.gov NCT03181360. EudraCT Number 2014-000096-80.

Keywords

Tenecteplase, wake-up stroke, acute ischemic stroke, intravenous thrombolysis, TWIST

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Introduction and rationale

Thrombolytic treatment with intravenous recombinant tissue plasminogen activator (rt-PA) given within 4.5 h of onset improves clinical outcome after ischemic stroke.[1] About one in five ischemic strokes occur during sleep,[2] and these strokes have traditionally been considered ineligible for thrombolytic treatment because the time of onset is unknown. Recent trials have found benefit of intravenous thrombolytic treatment with alteplase in patients with wake-up ischemic stroke (WUS) and mismatch in lesion visibility between diffusion-weighted imaging and fluid attenuation inversion recovery (DWI/FLAIR mismatch) on MRI or signs of penumbra on CT perfusion (CTP).[3,4] Although thrombolytic treatment has been shown to be effective in patients who fulfil advanced imaging criteria, it is possible that thrombolysis will benefit patients without such radiologic findings as well. Previous studies have shown that DWI/FLAIR mismatch can be absent in as many as 40% of patients with known stroke duration of less than 3 h,[5] indicating that selection of patients based on advanced imaging criteria could exclude WUS patients who might benefit from thrombolysis. One-third of patients who underwent screening for inclusion in the WAKE-UP trial were excluded because they did not fulfil mismatch criteria.[3] Previous studies have shown that clinical and radiological findings did not differ between patients with WUS and patients with stroke of known onset within 4.5 h.[6] The limited availability of emergency MRI and CTP in many hospitals may also prevent patients from receiving treatment. Thrombolytic treatment of WUS selected by non-contrast CT was found to be safe in two prospective, single-armed open-label trials.[7] A randomized-controlled trial using routinely available brain imaging criteria to select patients for treatment is therefore highly warranted.

Tenecteplase is genetically engineered to have pharmacological advantages over alteplase and has a simpler administration as it is given as a single bolus.[8] A recent meta-analysis of five randomized controlled trials showed strong evidence of tenecteplase being non-inferior to alteplase for acute ischemic stroke.[9] In one randomized trial, tenecteplase was associated with a higher incidence of reperfusion and improved clinical outcome compared to alteplase.[10]

The aims of TWIST are to answer the following questions:

- Can thrombolytic treatment with tenecteplase given within 4.5 h of waking up with ischemic stroke using non-contrast CT selection criteria improve functional outcome at three months?
- Can findings on non-contrast CT identify patients with wake-up ischemic stroke who benefit from such treatment?

Methods and design

TWIST is a pragmatic, CT-based prospective, randomized controlled, open-label trial with blinded end-point assessment of intravenous thrombolysis with tenecteplase in patients with acute ischemic stroke upon awakening.

Research ethics and regulatory approvals

The trial is conducted in accordance with the MRC Guidelines for Good Clinical Practice in Clinical Trials, the Council of Europe's Convention on Human rights and Biomedicine (CETS No.: 164), the ICH Harmonized Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95), and the Declaration of Helsinki (Edinburgh, October 2000). TWIST has received approval from medical research ethical committees and medical agencies in all 10 participating countries. Written, informed consent is obtained from all eligible patients according to approved national regulations.

Patient population

We aim to include 600 patients (300 in each treatment arm) with WUS who can be treated within 4.5 h after awakening.

Inclusion and exclusion criteria

Inclusion criteria (simplified)

- Clinical diagnosis of stroke upon awakening (symptoms not present before sleep) with (i) limb weakness and National Institutes of Health Stroke Scale (NIHSS) score $\geq$3, or (ii) dysphasia.
- Treatment with tenecteplase is possible within 4.5 h of awakening.

Exclusion criteria (simplified)

- Age <18 years.
- NIHSS score >25 or NIHSS consciousness score >2, or seizures.
- Findings on non-contrast CT that indicate the patient is unlikely to benefit from treatment:
  - Infarction comprising more than >1/3 of the middle cerebral artery territory.
  - Intracranial hemorrhage.
- Active internal bleeding or high risk of bleeding (e.g. major surgery, trauma, gastrointestinal or urinary tract hemorrhage within 21 days, arterial puncture at non-compressible site within 7 days, defect in coagulation, known defect of clotting or platelet function).

The complete list of inclusion and exclusion criteria is shown in Supplemental Material.

Randomization

Patients are randomized in a 1:1 ratio using a central computer-generated randomization schedule. The schedule employs a minimization algorithm including age, stroke severity (NIHSS), and time since wake-up and is set to balance these characteristics across all centres in all countries.

Intervention

The intervention group will be given tenecteplase 0.25 mg per kg of body weight (maximum 25 mg), as an intravenous bolus, plus standard care, while the control group will be given standard care without thrombolysis with tenecteplase or any other thrombolytic agent. Both treatment arms will receive best standard care, including intra-arterial interventions for proximal cerebral artery occlusion.

Clinical and radiological assessments

A timetable of clinical and radiological assessments is shown in Table 1.

Findings on baseline non-contrast CT that will be assessed are ASPECT Score, presence of early ischemic changes (loss of grey/white matter cortex definition, loss of basal ganglia outline, hypodensity, lesion volume), and hyperdense artery presence and localization.

Primary efficacy outcome

Functional outcome is defined by the mRS on the ordinal scale (0–6) at three months.

Information on modified Rankin Scale (mRS) at three months is obtained by centralized telephone interview by trained and mRS-certified personnel blinded for allocated treatment.

Secondary outcomes

Secondary effect outcomes include dichotomized mRS score (0–1 vs. 2–6 and mRS 0–2 vs. 3–6), death from all causes, symptomatic intracranial hemorrhage, any intracranial hemorrhage, major extracranial bleeding, recurrent ischemic stroke, NIHSS and change in NIHSS score from baseline, EuroQol score (EQ-5D-3L), mini-mental status examination score, and health-economic variables at three months, in addition to radiological outcomes at 24 h (see Supplemental Material for complete list).

Data monitoring body

The Data Monitoring Committee (DMC) is regularly performing unblinded reviews of SAEs in all patients. An independent statistician prepares the data reports. Only the DMC has access to the interim results. If evidence of harm, or evidence of efficacy, the committee will advise the chair of the Steering Committee.

Table 1. Examinations at baseline and follow-up

	Days							Months
	1					2	7[a]	3
	Time 1[b]	Time 2[c]	30 min	1 h	3 h			
Non-contrast CT	x			x			x	
CT angiography	(x)			x		(x)		
CT perfusion	(x)			(x)				
NIHSS	x					x	x	
BP monitoring	x	x	x	x	x	x		
mRS	x						x	x
Centralized telephone interview								x

Note: Day 1 is the day of entry into the trial.
[a]Day 7 or day of discharge, whichever occurs first.
[b]Time 1: at randomization.
[c]Time 2: at time of intervention/treatment.
BP: blood pressure; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; (x): optional examination which should not influence the decision to include the patient, unless the results of the examination, according to the judgment of the investigator, show that the patient should or should not receive thrombolytic treatment.

The DMC will also be responsible for monitoring the overall conduct of the trial, and may formulate recommendations to improve adherence to protocol, management, procedures, and quality control.

Sample size estimates

We assume a treatment effect of 10% absolute difference in a binary endpoint setting (mRS 0–1 vs. mRS 2–6) and a distribution between modified Rankin Scale categories similar to that of the WAKE-UP trial[3] with 42% with favourable outcome in the non-thrombolysed group versus 52% in the thrombolysed group, corresponding to an odds ratio of 1.50. Assuming an effect size specified as an odds ratio of 1.5 from an ordinal logistic regression model and similar distribution of mRS scores in the control group in six levels as in the WAKE-UP trial (categories 5 and 6 merged) of 15%, 27%, 23%, 17%, 13%, and 5%[3], the estimated sample size of 600 patients yields a power of 80%, with a two-sided significance level of 5%.

Statistical analyses

We will analyze the data according to the intention-to-treat principle. Functional outcome will be compared between the study groups by means of ordinal logistic regression and adjusted for age, stroke severity (baseline NIHSS), and time since wake-up. In secondary analyses, favourable outcome defined as mRS 0–1 will be compared by means of logistic regression with mRS 2–6, and good outcome defined as mRS 0–2 with mRS 3–6. A separate set of supplementary analyses will be performed stratified by patients who received endovascular treatment and those who did not.

For clinical event outcomes, we will estimate odds ratios and 95% confidence intervals using logistic regression and estimate hazard ratios with corresponding 95% confidence intervals using the Cox proportional hazards model. All analyses will use 5% two-sided level of significance. A detailed statistical analysis plan will be published prior to end of recruitment.

Study organization and funding

The University Hospital of North Norway is the Sponsor of the trial.

The main source of funding is from the Norwegian 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 covered by an unconditional grant from Boehringer Ingelheim Norway KS.

Discussion

TWIST includes patients with wake-up stroke selected by non-contrast CT and investigates whether these can benefit from intravenous tenecteplase. The effect of thrombolytic treatment in wake-up stroke patients without mismatch criteria on MRI or CTP has not been evaluated in previous randomized controlled clinical trials. Although the rationale for using the specific imaging criteria in the recent clinical trials of reperfusion therapy is well funded theoretically, this cannot be taken as evidence for lack of benefit from treatment in patients without such criteria. DWI/FLAIR mismatch can be absent in 40% of patients with known stroke duration of less than 3 h.[5] If treatment is offered only to patients fulfilling the imaging criteria of the recent studies, many patients who might benefit from treatment may be excluded. Furthermore, MRI is not available in the emergency setting in many hospitals, and selection based on non-contrast CT may increase access to treatment and reduce delays.

Tenecteplase may potentially improve recanalization compared to alteplase.[11] The bolus administration and the very rapid onset of action make tenecteplase an attractive option for stroke patients and might possibly reduce the time to recanalization of an occluded cerebral artery compared to alteplase.

We originally based our sample size estimation on the results of a Cochrane systematic review of the effect of rt-PA within 4.5 h of stroke onset,[7] assessed as a binary endpoint (favourable outcome mRS 0–2 versus mRS 3–6). As the primary endpoint in TWIST is mRS across the full ordinal scale (shift analysis), sample size estimation based on ordinal logistic regression analysis is more appropriate. The revised sample size estimation is based on observations from recent studies on thrombolytic treatment in patients with wake-up stroke.[12,13] Details are presented in the Supplemental Material. As a result of the revised sample size estimation, the target was increased from 500 to 600 patients. An even larger increase to account for stroke mimics has not been deemed feasible in light of drop in recruitment rate after the onset of the Covid-19 pandemic as well as limited funding.

The TWIST study population is expected to reflect real-life every day clinical practice. If successful, TWIST may substantially increase the proportion of WUS patients eligible for thrombolytic treatment.

Summary and conclusions

TWIST will show whether patients with wake-up stroke can be treated with tenecteplase within 4.5 h of awakening, and whether non-contrast CT can be used to identify patients who benefit from treatment.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The cost of tenecteplase is covered by an unconditional grant from Boehringer Ingelheim Norway KS.

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Supplemental material

Supplemental material for this article is available online.

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Supplemental Material

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TWIST Protocol version/date 200917

Trial Sponsor: University Hospital of North Norway, NO-9038 Tromsø, Norway

Telephone number: +47 77626000

Trial Registration

EudraCT Number, 2014-000096-80. ClinicalTrials.gov, NCT03181360.

Registered June 8, 2017.

We report the trial protocol in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. Please view submitted checklist.

Study organisation

Sponsor

The University Hospital of North Norway, Tromsø, Norway is the Sponsor of the trial.

The Trial Coordinating Centre is based at the University Hospital of North Norway and the Brain and Circulation Research Group at UiT The Arctic University of Norway. The Trial Coordinating Centre consists of the following persons: Trial Coordinating Investigator Ellisiv B. Mathiesen, Trial Manager Melinda B. Roaldsen, Trial officer Agnethe Eltoft, Assistant Trial Manager Mary-Helen Søyland, Trial IT Manager David Perry and Trial Research Nurse Tone Bratteng. Eivind Berge had a central role in the initiation, planning and implementation of the trial and was Trial Co-coordinating Investigator until his death in Feb. 2020.

Trial Statistician: Tom Wilsgaard.

Trial Steering Committee: Bent Indredavik (Chair), Thompson G. Robinson, David Werring, Arnstein Tveiten, Jesper Petersson, Hanne Christensen, Helle Iversen, Jukka Putaala, Janika Kõrv, Dalius Jatuzis, Gian Marco De Marchis, Stefan Engelter, Erik Lundström, Tom Wilsgaard and Ellisiv B. Mathiesen.

Independent Data Monitoring Committee: Terje Pedersen (Chair), Hans Wedel (statistician) and Peter Sandercock. An independent statistician, Ola Løvsletten, produces the unblinded statistical reports for the DMC.

Event Adjudication Committee: Centralized blinded evaluation of all events is performed by Stein-Harald Johnsen (Chair), Michael Mazya and Thomas Christensen.

Patient Advisory Board: Arne Hagen (the Norwegian Association for Stroke Survivors) and Anne Heimdal (LHL Stroke).

Image Analysis Centre: Centralized blinded evaluation of all radiological images is done by Andrew Bivard and Mark Parsons (Melbourne Brain Centre, University of Melbourne, Royal Melbourne Hospital, and the University of New South Wales, Australia).

Supplementary methods

Inclusion and exclusion criteria

Complete list of inclusion criteria

- Stroke symptoms on awakening that were not present before sleep
- Clinical diagnosis of stroke with limb weakness with 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 health care personnel), or written consent from the nearest family member

Complete list of exclusion criteria

- Age <18 years
- NIHSS score >25 or NIHSS consciousness score >2, or seizures during stroke onset
- Findings on plain CT that indicate that the patient is unlikely to benefit from treatment:
    - Infarction comprising more than >1/3 of the middle cerebral artery territory on plain CT or CT perfusion
    - Intracranial haemorrhage, structural brain lesions which can mimic stroke (e.g. cerebral tumour)
- Active internal bleeding or 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 idarusizumab) or with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, eucarin clotting time, TT, 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 can be included)
  - Ischaemic stroke or myocardial infarction in previous 3 months, previous intracranial haemorrhage, severe traumatic brain injury or intracranial or intraspinal operation in previous 3 months, or known intracranial neoplasm, arteriovenous malformation or aneurysm
- Contraindications to tenecteplase, e.g., acute bacterial endocarditis or pericarditis; acute pancreatitis; severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension; active hepatitis; systemic cancer with increased bleeding risk; haemostatic defect including secondary to severe hepatic, renal disease; organ biopsy; prolonged cardiopulmonary resuscitation > 2 min (within 2 weeks)
- Persistent blood pressure elevation (systolic ≥185 mmHg or diastolic ≥110 mmHg), despite blood pressure lowering treatment
- Blood glucose <2.7 or >20.0 mmol/L (use of finger-stick measurement devices is acceptable)
- Pregnancy, positive pregnancy test, childbirth during last 10 days, or breastfeeding. In any woman of childbearing potential, a pregnancy test must be performed and the result assessed before trial entry

- Other serious or life-threatening disease before the stroke: severe mental or physical disability (e.g. Mini Mental Status score <20, or mRS score ≥3), or life expectancy less than 12 months
- Patient unavailability for follow-up (e.g. no fixed address)

Standard care

Both the intervention group and the control group should be given best standard care, according to clinical guidelines. This includes intra-arterial interventions for proximal cerebral artery occlusion, when appropriate. If the patient is given tenecteplase, then aspirin or other antiplatelet or anticoagulant drugs shall not be given until 24 hours after termination of infusion and after the control CT brain scan. Patients allocated to control should receive aspirin 300 mg as a loading dose as soon as possible after randomization (unless there are contraindications to aspirin). After first 24 hours the recommended daily dose of aspirin is 75 mg once daily in both the tenecteplase group and the control group. Best standard care during the first week also include treatments to maintain normal homeostasis (temperature, blood glucose, hydration, nutrition), as well as lipid lowering and blood pressure lowering drugs, in accordance with clinical guidelines. Clinical examinations, including additional CT scans should be performed as clinically indicated.

Primary outcome (complete list)

Functional outcome (defined by the mRS) at 3 months

Secondary outcomes (complete list)

Clinical events:

- Favourable functional outcome: mRS 0-1
- Good functional outcome: mRS 0-2
- Death from all cause during follow-up
- Any intracranial haemorrhage during follow-up
- Symptomatic intracranial haemorrhage by SITS-MOST[1] definition
- Symptomatic intracranial haemorrhage by IST-3[2] definition
- Parenchymal haemorrhage type 2[3]
- 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 an day 7

Clinical events are defined in the Appendix.

Other clinical outcomes:

NIHSS score, Barthel Index score, EuroQol score, and MMSE scores at 3 months

Radiological outcomes will be defined in a separate imaging protocol.

Health-economic variables:

- Length of hospital stay
- Nursing home care after discharge
- Re-hospitalisations during first 3 months

Protocol amendments

Inclusion and exclusion criteria:

There have been two major amendments: changes to the inclusion and exclusion criteria (Protocol amendment July 4, 2018) and revision of the sample size estimation (Protocol amendment Sept 17, 2020). In the first major amendment, the inclusion criterion was changed from NIHSS score ≥5 to ≥3. The rationale for this is that many patients with wake-up stroke have mild stroke (low NIHSS score) with clinically relevant deficits, and therefore could be included. Further, we allowed inclusion of patients who were to be treated with intra-arterial interventions for proximal cerebral artery occlusion.

Sample size estimation:

We originally based our sample size estimation on the results of a Cochrane systematic review of the effect of rt-PA within 4.5 hours of stroke onset[4], assessed as a binary endpoint (favourable outcome mRS 0-2 versus mRS 3-6). As the primary endpoint in TWIST is mRS across the full ordinal scale (shift analysis), sample size estimation based on ordinal logistic regression analysis is more appropriate. The revised sample size estimation is based on observations from recent studies on thrombolytic treatment in patients with wake-up stroke[5, 6].

In the largest randomized controlled trial on wake-up strokes, WAKE-UP, the difference between thrombolysed and non-thrombolysed patients was 11,5% for a favourable outcome defined as mRS 0-1. A difference of 11,5% was also found in a recent meta-analysis of six observational studies on patients with unknown stroke onset time, where favourable outcome was defines as mRS 0-2. The MRI-based inclusion criteria in WAKE-UP compared to the CT-based inclusion of TWIST could lead to smaller treatment effect in TWIST. We assume a treatment effect of 10% absolute difference in a binary endpoint setting (mRS 0-1 versus mRS 2-6) and a distribution between mRS categories similar to that of the WAKE-UP trial[7] with 42% with favourable outcome in the non-thrombolysed group vs 52% in the thrombolysed

group, which corresponds to an odds ratio of 1.50, and mRS distribution in the control group in six levels (categories 5 and 6 merged) as 15%, 27%, 23%, 17%, 13%, 5%. With a power of 80%, a two-sided significance level of 5%, and an effect size specified as an odds ratio of 1.50 from an ordinal logistic regression model for the ordinal outcome in the control group, the estimated sample size is 600. T, the revised target is to recruit 600 patients, i.e. 300 patients in each arm.

A complete list of amendments is available in the protocol (*https://twist.uit.no)*

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3. von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, et al. The Heidelberg bleeding classification: Classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46:2981-2986
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5. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, et al. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. *N Engl J Med*. 2018
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Appendix I

Appendix I. The Modified Rankin Scale

	mRS	Description
Independent	0	No symptoms at all
	1	No significant disability. Able to carry out all usual duties and activities, despite symptoms
	2	Slight disability. Unable to perform all previous activities but able to look after own affairs without assistance
Dependent	3	Moderate disability. Requires some help, but able to walk without assistance
	4	Moderately severe disability. Unable to attend to own bodily needs without assistance, unable to walk without assistance and unable to take care of own affairs
	5	Severe disability. Bedridden, incontinent, requiring constant nursing care and attention
Dead	6	

Appendix II

Appendix II. Oxford Handicap Score

Handicap	Lifestyle	Grade
none	no change	0
minor symptoms	no interference	1
minor handicap	some restrictions but able to look after self	2
moderate handicap	significant restriction; unable to lead a totally independent existence (requires some assistance)	3
moderate-to-severe handicap	unable to live independently but does not require constant attention	4
severe handicap	totally dependent; requires constant attention day and night	5