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[Intervention Review]

Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke

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ABSTRACT

Background

Stroke is a leading cause of death and disability world wide. Thrombolysis with recombinant tissue plasminogen activator (rt-PA) is licensed for treatment of acute ischaemic stroke in the early hours after symptom onset. It has been shown in randomised controlled trials (RCTs) and the 2009 Cochrane review of thrombolysis for acute ischaemic stroke to reduce dependency but at the increased risk of intracranial haemorrhage. Methods to reduce the risk of haemorrhage while retaining or enhancing the benefit could increase the use of thrombolytic treatment. While most available information comes from RCTs of intravenous rt-PA at 0.9 mg/kg, it is possible that other doses, drugs and other routes of administration might increase benefit and reduce the hazard.

Objectives

To assess the risks and benefits of different thrombolytic agents, doses and routes of administration for the treatment of acute ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (May 2012), MEDLINE (1966 to May 2012) and EMBASE (1980 to May 2012). We handsearched journals and conference proceedings, searched ongoing trials registers and contacted pharmaceutical companies and researchers.

Selection criteria

Unconfounded randomised and quasi-randomised trials of different doses of a thrombolytic agent, or different agents, or the same agent given by different routes, in people with confirmed acute ischaemic stroke.

Data collection and analysis

Two review authors independently assessed trial eligibility and quality, and extracted the data using a structured proforma. We cross-checked and resolved discrepancies by discussion to reach consensus. We obtained translations and additional information from study authors where required.

Main results

We included 20 trials involving 2527 patients. Concealment of allocation was poorly described. Different doses (of tissue plasminogen activator, urokinase, desmoteplase or tenecteplase) were compared in 13 trials (N = 1433 patients). Different agents (tissue plasminogen activator versus urokinase, tissue-cultured urokinase versus conventional urokinase, tenecteplase versus tissue plasminogen activator)

were compared in five trials (N = 875 patients). Five trials (N = 485) compared different routes of administration. As some trials compared different agents and different doses, some patients contributed to two analyses. There was an approximately three-fold increase in fatal intracranial haemorrhages in patients allocated to higher than to lower doses of the same thrombolytic drug (odds ratio (OR) 2.71, 95% confidence interval (CI) 1.22 to 6.04). There was no difference in the number of patients who were dead or dependent at the end of follow-up between those allocated higher or lower doses of thrombolytic drug (OR 0.86, 95% CI 0.62 to 1.19). Higher versus lower doses of desmoteplase were associated with more deaths at the end of follow-up (OR 3.21, 95% CI 1.23 to 8.39). There was no evidence of any benefit for intra-arterial over intravenous treatment.

Authors' conclusions

These limited data suggest that higher doses of thrombolytic agents may lead to higher rates of bleeding. However, the evidence is inadequate to conclude whether lower doses of thrombolytic agents are more effective than higher doses, or whether one agent is better than another, or which route of administration is the best, for acute ischaemic stroke. At present, intravenous rt-PA at 0.9mg/kg as licensed in many countries appears to represent best practice and other drugs, doses or routes of administration should only be used in randomised controlled trials.

PLAIN LANGUAGE SUMMARY

Clot-dissolving drugs (different doses, routes of administration and agents) for breaking down a blood clot blocking a blood vessel in the brain

Many strokes are due to a sudden blockage of an artery in the brain. Treatments to dissolve the clot (also called thrombolytic treatment) can improve the chance of making a good recovery from a stroke. This review aimed to find out if there were important differences between different clot-dissolving drugs. It also aimed to find out if there were differences in effect when giving the same drug in different doses or by different routes (into an artery or a vein). The review, which included 20 studies involving 2527 participants, showed that there was some evidence that lower doses of thrombolytic agents led to serious bleeding in the brain less often. However, it was not clear if the benefit from lower doses was as big as with higher doses. There was no evidence to show that one thrombolytic agent was clearly better than another, or that intra-arterial treatment was better than intravenous treatment. Therefore, more larger randomised controlled trials are required to answer questions about which drug, or dose or route of administration is best for thrombolysis. At present, rt-PA as currently licensed in many countries, should be regarded as best practice.

BACKGROUND

Description of the condition

Stroke is a leading cause of death and disability world wide. Most strokes are ischaemic and due to a thrombotic or embolic occlusion of an intracranial artery. Rapid administration of intravenous thrombolytic therapy with the drug recombinant tissue plasminogen activator (rt-PA, generic name alteplase) is the principal treatment in the early hours after the onset of symptoms and has been shown in randomised controlled trials (RCTs) to improve outcomes (Wardlaw 2012; additional information in Hacke 2004 and Lees 2010). Although rt-PA is the only thrombolytic drug licensed for the treatment of acute ischaemic stroke, other thrombolytic drugs have also shown promise (Wardlaw 2009; Wardlaw 2010). The earlier the thrombolytic agent is administered the more patients remain alive and independent (Lees 2010; Wardlaw 2012). However, the major risk of the treatment is intracranial haemorrhage, which is the single most frequent cause of death following thrombolysis regardless of which drug is used (Wardlaw 2009; Wardlaw 2010; Wardlaw 2012). Systemic bleeding is a less common but potentially serious complication.

Description of the intervention

Most of the randomised controlled trials (RCTs) of thrombolytic drugs to date have tested intravenous rt-PA but other routes of administration, drugs or doses of drug might reduce hazard or be more beneficial. Intra-arterial thrombolysis offers some theoretical advantages such as regionally localised therapy, reduced overall dose and hence systemic effects of thrombolytic therapy. However, this comes at the cost of a more invasive technique, delay in treatment initiation and the requirement for a specialised radiological unit. Despite this, in recent years there has been increasing interest in intra-arterial therapy and also in mechanical devices to extract the intraluminal clot with or without the use of pharmacological thrombolysis (Lee 2010; Lindsberg 2006; Lisboa 2002; RECANALISE 2009). However, there are as yet no completed randomised trials testing mechanical devices, although some are expected to start soon.

Apart from rt-PA, other thrombolytic drugs have also been tested in stroke. Two RCTs testing streptokinase were terminated early due to a high rate of symptomatic haemorrhage and a third was stopped due to the adverse climate generated by termination of the other two, although the third trial had not demonstrated any excess hazard (Wardlaw 2009; Wardlaw 2010). Urokinase has been used in the treatment of stroke, although less often recently. Newer thrombolytic agents, such as tenecteplase and desmoteplase, are variants of the native plasminogen activators and are currently being evaluated as alternative fibrinolytic agents.

How the intervention might work

Alternative routes of administration, drugs or doses might reduce hazard whilst preserving benefit. Amongst trials mostly comparing intravenous thrombolysis with control (summarised in Wardlaw 2009; Wardlaw 2010), there was marked heterogeneity in case fatality rates. It was possible to explore reasons for the heterogeneity only in a very limited way but several points emerged. For example, the case fatality at the end of follow-up in the thrombolysis-treated patients was lower in the trials that tested lower doses of thrombolytic drug than in the trials that tested doses similar to those used to treat acute myocardial infarction (MI),

although the difference was not statistically significant and there was no obvious trend in case fatality between the trials using the lowest and highest doses. There are of course many other reasons for the between-trial heterogeneity.

Why it is important to do this review

The available data on the use of thrombolytic drugs to treat acute ischaemic stroke have posed questions for further research. Do lower doses of thrombolytic drugs reduce the hazard without compromising the benefit? Which thrombolytic drug has the least hazard and most benefit or are they all the same? Which is the best route of administration: intravenous, intra-arterial or other?

Recently, with the development of several newer thrombolytic drugs, there have been more trials testing different doses and comparing different drugs with the licensed drug rt-PA. We updated this systematic review to identify what information there is concerning choice of thrombolytic drug, dose and route of administration for treating acute ischaemic stroke. We sought to identify which, if any, regimen might have the most benefit and least hazard in acute ischaemic stroke, and highlight where more trials are needed.

OBJECTIVES

The aims of this review were as follows.

1. To compare a higher dose with a lower dose of thrombolytic therapy to determine whether there are important differences in:
 - a. the proportion with poor long-term outcome (efficacy);
 - b. the number of early deaths (safety);
 - c. the number of deaths by the end of the scheduled follow-up period (safety); and
 - d. symptomatic (including fatal) intracranial haemorrhage (safety).
2. To compare one thrombolytic agent with an equivalent dose of another agent to see whether there are important differences in:
 - a. the proportion with poor long-term outcome (efficacy);
 - b. the number of early deaths (safety);
 - c. the number of deaths by the end of the scheduled follow-up period (safety); and
 - d. symptomatic (including fatal) intracranial haemorrhage (safety).
3. To compare intravenous with intra-arterial thrombolysis (with the same agent) to see whether there are important differences in:
 - a. the proportion with poor long-term outcome (efficacy);
 - b. the number of early deaths (safety);
 - c. the number of deaths by the end of the scheduled follow-up period (safety); and
 - d. symptomatic (including fatal) intracranial haemorrhage (safety).

The primary outcome in this review was poor functional outcome at the end of follow-up. We considered early and total deaths at the end of follow-up, symptomatic and fatal intracranial haemorrhages and major extracranial haemorrhages to be secondary outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All unconfounded truly randomised or quasi-randomised trials in patients with acute ischaemic stroke within 14 days of stroke onset in which:

1. a lower dose of the thrombolytic agent was compared with a higher dose of the same agent; or
2. one thrombolytic agent was compared with another agent; or
3. two different routes of administration of the same agent were compared.

We included trials that had a placebo group as well as two groups receiving different doses of the same thrombolytic agent, but the placebo patients do not appear in this review. Trials comparing thrombolysis with placebo are presented in the Cochrane review of 'Thrombolysis for acute ischaemic stroke' (Wardlaw 2009; Wardlaw 2010).

Types of participants

Trials which included patients of any age or sex within 14 days of onset of acute ischaemic stroke (pre-randomisation computerised tomography (CT) or magnetic resonance imaging (MRI) having excluded cerebral haemorrhage as the cause of symptoms) were eligible. Although it is likely that thrombolysis is most effective if given within the first few hours of stroke, we have included trials treating patients at comparatively late stages in this version of the review because, in general, the trials that treated patients late were testing very low doses - i.e. a different approach to the use of thrombolysis and there was no good logical reason for excluding these trials at this stage. In future, should more data become available, it will be possible to conduct sensitivity analyses of early high-dose versus later lower-dose treatment.

Types of interventions

We included trials that tested, in a randomised design, any type of thrombolytic drug - urokinase (UK), pro-urokinase (PRO-UK), streptokinase (SK), recombinant and tissue plasminogen activator (rt-PA and t-PA respectively), tenecteplase (TNK), desmoteplase, retevase or lumbrokinase (LK) - either in different doses (e.g. lower dose of half to two-thirds of that of a higher dose) or by different administrative methods (of the same drug) or comparing different drugs to treat acute ischaemic stroke. The drugs could be given intravenously, intra-arterially or orally (where appropriate). We excluded confounded trials (e.g. lower dose of thrombolytic drugs plus another agent versus higher dose of thrombolytic drug).

Types of outcome measures

We considered five main outcomes.

Primary outcomes

Poor functional outcome at the end of follow-up (where follow-up was performed at one month or longer after the stroke). This was defined as death or dependency on others in activities of daily living, at the end of the trial follow-up period where this was one month or later after the stroke (although we accept that

dependency measured earlier than three months may not allow sufficient time for maximum recovery to have occurred).

Secondary outcomes

1. Death from any cause and vascular/unknown death (a) within the first two weeks of treatment, and (b) during the whole trial follow-up period (we included trials with final follow-up at one month or longer).
2. Intracranial haemorrhage: symptomatic (i.e. associated with a deterioration in the patient's neurological state) and fatal (i.e. leading directly to the death of the patient). Intracranial haemorrhage includes haemorrhagic transformation of the infarct, haemorrhage elsewhere in the brain, and haemorrhage into the spaces surrounding the brain.
3. Major extracranial haemorrhage (i.e. fatal or requiring a transfusion or an operation).
4. Other major extracranial events (e.g. deep vein thrombosis (DVT), ischaemic leg and haematoma at the puncture site following angiography).

Search methods for identification of studies

See the 'Specialized register' section in the [Cochrane Stroke Group](#) module. We searched for relevant trials in all languages and arranged translation of trial reports published in languages other than English.

Electronic searches

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor in May 2012. We also searched MEDLINE (1966 to May 2012) ([Appendix 1](#)) and EMBASE (1980 to May 2012) ([Appendix 2](#)). We included trials known to be completed and published by February 2013.

We sought Information from the Stroke Trials Registry (www.strokecenter.org/trials), ClinicalTrials.gov (www.clinicaltrials.gov/), EU Clinical Trials Register (www.clinicaltrialsregister.eu), Current Controlled Trials (www.controlled-trials.com) and the WHO International Clinical trials Registry Platform (<http://apps.who.int/trialsearch/>). We used Google to search for individual trial names and then searched any online resources of the relevant trials (e.g. trials websites).

Searching other resources

We handsearched the following journals from 1979 to April 1994 for the first review: *Japanese Journal of Stroke*; *Clinical Evaluation*; *Japanese Journal of Pharmacology & Therapeutics*; *Rinsho Ketsueki*. We obtained translations of the non-English language publications from people in whose native language the paper was published. For the latest update of the review, and in order to validate the results of the MEDLINE and EMBASE searches, we handsearched three journals (*American Journal of Neuroradiology*, *New England Journal of Medicine* and *Stroke*) from January 2006 to December 2010.

In 1997 we contacted all pharmaceutical companies listed in the British National Formulary (BNF) and the Monthly Index of Medical Specialties (MIMS) for more information about trials, both those known to exist from the above efforts, and any trials which were unknown to the review authors. Only one company, Genentech, an American company, did not respond. For the previous update

we contacted Gruenenthal for trial details. We did not contact any other companies for this update.

We searched the abstracts presented at international conferences for acute stroke (the European Stroke Conferences 1991 to 2012, the biennial International Symposia on Thrombolysis in Acute Ischaemic Stroke 1992 to 2011, the biennial World Stroke Conferences 2000 to 2012, and the American Heart Association International Stroke Conferences 1990 to 2013). We also searched abstracts of other neurological and cerebrovascular symposia as published in journals and through colleagues who attended.

We contacted the principal investigators of trials in Europe, the USA, Japan and China when we required additional information.

Data collection and analysis

Selection of studies

For the update of this review two authors (PK, JMW) independently screened titles and abstracts, excluded obviously irrelevant articles and selected trials for inclusion in the review. We resolved any disagreements by discussion. We obtained the full text of the remaining articles and the same two authors independently selected studies meeting the inclusion criteria. We resolved any further disagreements by discussion if necessary. One author (PK) extracted data on the methodological quality and outcome assessments. The other author (JMW) cross-checked all the extracted data and we resolved differences by discussion if necessary.

Data extraction and management

Review authors extracted data by using a standard proforma (ML and JMW for trials included in the previous version of the review; PK and JMW for trials identified since the last version of this review). The review authors resolved disagreements by discussion or by correspondence with the trial authors. For the most recent update, PK entered data into Review Manager ([RevMan 2011](#)) and JMW checked the data.

Assessment of risk of bias in included studies

We collected information about the method of randomisation, allocation concealment, blinding (both of treatment administration and of outcome assessment), whether an intention-to-treat analysis was done or could possibly be done and the number of patients who were lost to follow-up, to assess the methodological quality and risk of bias in the included studies ([Higgins 2011](#)).

Measures of treatment effect

For outcome assessment we extracted the number of patients originally allocated to each treatment group irrespective of compliance to allow an intention-to-treat analysis (trials that included a placebo group are included in the present review, but the placebo patients are included in the Cochrane review of 'Thrombolysis for acute ischaemic stroke' ([Wardlaw 2009](#); [Wardlaw 2010](#)), and trials of rt-PA are published in the 2012 systematic review ([Wardlaw 2012](#)), not in this review).

We then collected the number of patients who:

1. died in the early stage (within the first two weeks of the stroke) and by the end of the trial follow-up;

2. were disabled (dependent on others in activities of daily living) by the end of the trial follow-up period. We defined dependency as a score of three to five on the modified Rankin Scale (mRS) (or equivalent);
3. developed symptomatic or fatal intracranial haemorrhage (confirmed by CT or MR or post mortem) in the acute stage. We defined symptomatic intracranial haemorrhage as intracranial haemorrhage, confirmed by a CT, MR scan, lumbar puncture or autopsy, accompanied by deterioration in the neurological condition of the patient. Fatal intracranial haemorrhage is death attributed to intracranial haemorrhage confirmed by CT or MR brain imaging or post mortem examination. There is a problem with the estimation of the true number of symptomatic or fatal intracranial haemorrhages because some patients died without a CT or MR scan or post mortem. Patients who died in the acute stage of neurological causes may have had an intracranial haemorrhage, so we collected the number of patients who had symptomatic intracranial haemorrhage or who died in the acute stage to avoid underestimation of major intracerebral haemorrhage;
4. had major extracranial haemorrhage, defined as haemorrhage outside the cranial cavity that resulted in clinical deterioration of the patient, prolonged immobility or stay in hospital, or required transfusion or surgical evacuation;
5. had complications that might be a consequence of the administration route, e.g. groin haematoma or limb ischaemia following angiography.

Unit of analysis issues

We used mRS scores where available. Where not available we converted other relevant stroke scales to the mRS. Where it was not possible to convert, or where functional outcome was not assessed, we omitted the trial from analysis of functional outcome. The only other outcome where there was potential for variable measures was symptomatic intracranial haemorrhage. Here we used the trial-specific definition and did not attempt to convert these to some other standard as there is no consensus on how symptomatic intracranial haemorrhage should be standardised, nor did the trials provide information to allow any conversion.

Dealing with missing data

We sought missing data from trial investigators and any other associated contacts. If it was not possible to obtain data omitted from the trial publication, we omitted the trial from that analysis. These are highlighted in the results section. We have used all available data.

Assessment of heterogeneity

We assessed heterogeneity using the I^2 statistic. We also reported the χ^2 test in the tables and figures ([APT 1994](#)).

Assessment of reporting biases

We assessed reporting biases using funnel plots.

Data synthesis

We calculated the Peto odds ratios for each outcome.

Subgroup analysis and investigation of heterogeneity

We also attempted to collect information on baseline characteristics of the patients, such as the severity of the stroke at randomisation, age of the patients, gender, etc. We hoped to be able to perform subgroup analyses based on these characteristics should the data be sufficient.

Sensitivity analysis

The main analyses were based on all trials. However, we also planned a priori sensitivity analyses based on:

1. trials with well-concealed treatment allocation (i.e. allocation was given by telephoning a central office; by first entering the data into a computer; by the pharmacy; by using identical numbered containers; or by sequentially numbered, sealed, opaque envelopes) versus less well concealed allocation;
2. trials with blinded outcome assessment versus unblinded assessment.

RESULTS

Description of studies

Results of the search

The searches of the Cochrane Stroke Group Trials Register, MEDLINE and EMBASE yielded 3672 potentially relevant abstracts but the majority were either completely irrelevant or excluded through being non-randomised comparisons, not testing comparisons relevant to this review, randomised but no relevant outcome reported, or confounded by another drug or intervention. Of these, 71 were relevant enough to be listed in the excluded studies section, five are ongoing, one is awaiting assessment but may prove to be irrelevant and 20 met the inclusion criteria.

Five trials ([BASICS](#); [DIAS-J](#); [ENCHANTED](#); [FRALYSE](#); [ITAIS](#)) are classified as ongoing. One further study ([Wadia 2009](#)) appears relevant to the topic of this review as it tests two different doses of tenecteplase but it has only been published in abstract so far and further information is required, particularly regarding the method of randomisation, and is therefore classified as awaiting evaluation.

Included studies

We included 20 trials involving 2527 patients, of which 13 trials (1433 patients) were relevant to the comparison of higher dose with lower dose, five trials (875 patients) to one agent versus another and five trials (485 patients) to different routes of administration. Three of these trials ([Abe 1990](#); [Parsons 2012](#); [TNK-S2B](#)) compared both different doses (259 patients) and different agents (341 patients). Thus, there was an overlap for the number of included trials and patients. Summary details of the included trials are given in the [Characteristics of included studies](#) table including, where available, data on baseline characteristics of the included patients.

Thirteen trials compared a higher dose of a thrombolytic drug with a lower dose of the same drug, of which five trials ([Abe 1990](#); [Kikuchi 1994](#); [Mori 1992](#); [Ohtomo 1988a](#); [Wang 2003](#)) tested t-PA, three trials ([Abe 1981](#); [Atarashi 1985](#); [Chen 2002](#)) tested UK, three trials ([DEDAS](#); [DIAS-2](#); [DIAS 2005](#)) tested desmoteplase, and two trials ([Parsons 2012](#); [TNK-S2B](#)) tested tenecteplase. Two trials ([Kikuchi 1994](#); [Mori 1992](#)) compared rt-PA (alteplase) 30 MIU (equivalent to 60 mg alteplase) with 20 MIU (40 mg) given by intravenous

infusion for one hour. [Abe 1990](#) compared rt-PA 2 MU with 1 MU/day intravenously over one hour once per day for seven days. [Ohtomo 1988a](#) compared t-PA 60,000 U with 36,000 U/day intravenously over one hour once per day for seven days. [Abe 1981](#) compared 60,000 U UK/day with 6000 U, [Atarashi 1985](#) compared 240,000 U UK per day with 60,000 U/day - in both trials the UK was given intravenously over one hour once per day for seven days. Only [Chen 2002](#) used UK in doses of 1 million units compared to 1.5 million units given within 30 minutes, i.e. in a manner compatible with other recent trials testing thrombolysis versus placebo in acute ischaemic stroke. In the case of the DIAS study where more than two regimens were evaluated, only the doses 125 µg/kg versus 90 µg/kg have been included in the analysis. The small numbers in the other dose groups make further statistical analysis meaningless at this stage. In [DEDAS](#) there were 12 protocol violations (six had no perfusion diffusion mismatch and six had internal carotid artery occlusions, which was an exclusion criterion; two in the placebo group, six in the low-dose and four in the high-dose group); for the purpose of this review we included these patients in the analysis. The DIAS study was a phase II dose finding study and several doses were tested; in the data analysis in this review we have only included the doses 125 µg/kg versus 90 µg/kg. In the two trials of tenecteplase ([Parsons 2012](#); [TNK-S2B](#)) the dose 0.25 mg/kg TNK is defined as the high-dose group and the 0.1 mg/kg TNK as the low-dose group. The 0.4 mg/kg TNK group in [TNK-S2B](#) had the lowest numbers, was eliminated early from the trial as inferior to the other two and has not been included in the statistical results.

Five trials tested different drugs - two compared t-PA with UK ([Abe 1990](#); [Ohtomo 1988b](#)), one compared tissue-cultured UK with UK ([Ohtomo 1985](#)) and two tested different doses of tenecteplase with rt-PA ([Parsons 2012](#); [TNK-S2B](#)). [Abe \(Abe 1990\)](#) compared a higher dose of rt-PA with a lower dose of t-PA and with UK. We have used the data from the higher-dose (2 MU/day) rt-PA group to compare with the UK group (60,000 IU) because of their dose similarity (as judged by dose equivalence for the treatment of acute MI). The tenecteplase trials ([Parsons 2012](#); [TNK-S2B](#)) compared two or three different doses of tenecteplase as well as rt-PA with tenecteplase. We extracted data comparing rt-PA against all doses of TNK as the optimal dose of TNK in the treatment of stroke is not known at this stage and the analysis could be updated in the future in the light of further evidence.

Five trials compared two different routes of administration, four ([EMS Bridging Trial](#); [Sen 2008](#); [SYNTHESIS](#); [SYNTHESIS EXPANSION](#)) tested rt-PA and one ([Ducrocq 2005](#)) tested UK. The EMS Bridging Trial compared intravenous rt-PA plus intra-arterial rt-PA with intravenous placebo plus intra-arterial rt-PA in a pilot study of 35 patients ([EMS Bridging Trial](#)). [Ducrocq 2005](#) is a single-centre, randomised trial comparing intravenous versus intra-arterial UK and had enrolled 27 patients before the study was terminated early due to the high mortality rate. [Sen 2008](#) conducted a feasibility study comparing intravenous (N = 4) versus intra-arterial (N = 3) rt-PA in patients with acute ischaemic stroke and major vessel occlusion on CT angiogram. [SYNTHESIS](#) was another pilot study evaluating intra-arterial t-PA up to six hours (N = 25 participants randomised, 19 treated) versus intravenous t-PA up to three hours (N = 29 participants randomised, 28 treated). Mechanical thrombus disruption or clot retrieval was allowed (used in 8/19 patients) but not balloon angioplasty. [SYNTHESIS EXPANSION](#) (N = 362), similar to like [SYNTHESIS](#), compared intra-arterial with intravenous rt-PA up to 4.5 hours after stroke. Mechanical devices

were allowed (in patients allocated intra-arterial therapy, 109/181 had clot fragmentation with a guidewire in addition to rt-PA and a device was used in 56/181 patients). The technique of thrombolytic delivery, mechanical clot disruption or clot extraction and the exact dose of fibrinolytic agent may differ substantially between patients, operators and trials. However, such differences are difficult to account for in the statistical analysis, especially when the data are so scant. The rt-PA in the [SYNTHESIS](#) and [SYNTHESIS EXPANSION](#) trials was administered as an infusion while in the other two newly included studies the thrombolytic agent was administered with what is described as the 'pulse spray' method. Whether or not this makes a practical difference is not known. Different doses of heparin are routinely administered during the intra-arterial treatment, further confounding the results. Blinding of patients and doctors to treatment is challenging in the interventional studies, increasing the risk for further bias.

Excluded studies

We excluded 71 studies because they were either: irrelevant to the current review, lacked randomisation or were confounded by the use of additional agents such as ultrasound or other drugs (see details below and the [Characteristics of excluded studies](#) table). We excluded some studies because they were confounded by different time windows ([Bu 1998](#); [Lee 1994](#)), or confounded by concomitant heparin doses ([Tazaki 1987](#); [Tsuchiya 1989](#); [Tsuchiya 1990](#)), or were stopped after only a few patients had been included ([Riedel 1996](#)),

or were studies of haematological effects of thrombolysis with no clinical outcome assessments ([Gao 1994](#); [Tazaki 1987](#); [Xu 2000](#)). The six non-randomised dose-escalation studies were [Del Zoppo 1989](#), [Morris 2003](#), [Qureshi 2002](#), [ReoPro Retavase MRI](#), [TASS](#) and [Yoneda 1998](#). Two trials ([Konta 1996](#); [Wu 1995](#)), which were awaiting assessment, have now been excluded because, to the best of our knowledge, the data have still not been published in full after five years.

In the process of doing this update we identified several studies that are relevant to the topic of this review but we excluded them because they did not fulfil the inclusion criteria. For example, [TTT-AIS](#) compares two different doses of rt-PA (standard dose 0.90 mg/kg versus 0.72 mg/kg), but it is not a randomised study. [J-ACT](#) tests the efficacy of 0.6 mg/kg rt-PA in acute stroke in the Japanese population (contrary to the widely used 0.9 mg/kg); we also excluded this single-arm, non-randomised trial, and a further registry ([J-MARS 2010](#)), from the review. [ITAIS-II](#) is testing the use of CT perfusion and angiography imaging to select patients for thrombolysis but is not a randomised drug comparison. Microplasmin ([MITI-IV](#)) is a truncated form of plasmin, has an extremely short half life when given intravenously and is not considered to be a true thrombolytic drug, so we also excluded it.

Risk of bias in included studies

The risk of bias in included studies is summarised in [Figure 1](#).

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

Details about concealment of randomisation were generally scant, so it is difficult to tell how adequate this was. All older trials used sequentially numbered containers for randomisation except two trials ([Abe 1981](#); [Abe 1990](#)), in which it was unclear whether the containers were sequentially numbered or not. Some of the more recent trials used central telephone randomisation ([DEDAS](#); [DIAS 2005](#); [TNK-S2B](#)) though others used sealed pre-packed drugs or sequential numbered envelopes.

Blinding

Most trials were double-blind so patients and doctors (including the outcome assessors) who treated the patients were blinded. However, some trials were open-label ([Sen 2008](#); [SYNTHESIS](#); [SYNTHESIS EXPANSION](#)) or conducted in few centres with local outcome assessors ([Ducrocq 2005](#)), making it difficult to blind the clinical outcomes to treatment allocation even if the assessments were said to be performed without knowledge of treatment allocation. In [SYNTHESIS EXPANSION](#), 90-day follow-up was by a single neurologist by telephone blinded to treatment allocation.

Incomplete outcome data

After consultation with the trial authors, we excluded few studies because of missing data where the data had been collected in the first place. A more major problem was that many trials did not collect data on functional outcome or symptomatic intracerebral haemorrhage and we therefore excluded them. Details of these are listed in the relevant sections. Most of these studies were small and likely to be methodologically weak for other reasons.

Selective reporting

We did not find any evidence of selective reporting bias.

Other potential sources of bias

No serious imbalance in baseline prognostic factors was reported between treatment groups, although in two trials there were more male patients in the lower-dose group, and in one trial ([EMS Bridging Trial](#)) there were more severe strokes and occluded arteries on angiography in the patients randomised to intravenous plus intra-arterial rt-PA than to intravenous placebo plus intra-arterial rt-PA. Intention-to-treat analyses were not reported in all trials but the data in all trials were sufficient to allow us to perform an intention-to-treat analysis in this review.

Other methodological factors

There is marked heterogeneity in the included studies as practices have changed over the last 30 years. The trial methodology and published data of the studies included in the last update are more standardised when compared with the earlier studies of this review: they now typically contain basic information on baseline stroke characteristics and the 90-day modified Rankin Scale. Seven of the early trials aimed to include patients with cerebral thrombosis, but most did not define what that was. One trial ([Mori 1992](#)) aimed to include thromboembolic stroke (source unspecified) of the internal carotid artery territory. Two trials used intra-arterial angiography to document the presence of thrombus in a cerebral artery ([EMS Bridging Trial](#); [Mori 1992](#)). One trial ([Kikuchi 1994](#)) aimed to include only patients with cerebral embolism (source unspecified). All the patients had a CT brain scan to exclude intracranial haemorrhage prior to randomisation. Most trials ([Chen 2002](#); [Ducrocq 2005](#); [EMS Bridging Trial](#); [Kikuchi 1994](#); [Mori 1992](#); [Parsons 2012](#); [Sen 2008](#); [SYNTHESIS](#); [TNK-S2B](#); [Wang 2003](#)) entered patients within six hours of stroke onset. Three studies ([DEDAS](#); [DIAS-2](#); [DIAS 2005](#)) extended this window to nine hours if there was more than 20% potentially salvageable tissue suggested by perfusion imaging (CT or MR). Five trials entered patients within three to five days and one trial ([Abe 1981](#)) within 14 days. One trial ([Mori 1992](#)) excluded patients with visible early infarction on the pre-randomisation CT scan. One tenecteplase trial ([Parsons 2012](#)) only included patients with a perfusion lesion on CT perfusion imaging that was 20% larger than the infarct core and an associated arterial occlusion on CT angiography pre-randomisation.

In the early studies, it was not possible to extract much information on the baseline characteristics of the patients or the relation to treatment outcome. For example, [Kikuchi 1994](#) used the Hemispheric Stroke Scale (HSS) to classify patients at randomisation (32% of the group given 30 MIU t-PA, and 37% of those given 20 MIU t-PA, were HSS 1 to 60), but it was not possible to relate these data to outcome following treatment. However, all the new studies included in the latest update

contained baseline and post-treatment characteristics such as stroke severity scores and functional outcome at the end of follow-up for each treatment group. In the [EMS Bridging Trial](#), there were more patients with severe strokes (and also more patients with occlusive thrombus in the intracranial arteries on angiography) in the patients randomised to intravenous plus intra-arterial rt-PA than in those randomised to intravenous placebo plus intra-arterial rt-PA ([EMS Bridging Trial](#)). In [SYNTHESIS](#), six of the 25 patients randomised to intra-arterial thrombolysis did not receive any treatment (no vessel occlusion, five of the six patients improved spontaneously); this compares with one of the 29 patients randomised to intravenous thrombolysis that improved spontaneously. In [SYNTHESIS EXPANSION](#), 15/181 patients allocated to intra-arterial treatment did not receive it (six improved clinically, three had no occlusion, three were dissections, one had a bleeding diathesis, one groin haematoma, one due to the delayed arrival of the interventionist) versus 3/181 allocated to intravenous treatment (one spontaneously improved, two had thrombectomy).

Antithrombotic drugs were not allowed during the whole study period in five trials ([Abe 1981](#); [Atarashi 1985](#); [Ohtomo 1985](#); [Ohtomo 1988a](#); [Ohtomo 1988b](#)) although an exception could be made if the doctors thought that antithrombotic drugs were needed. Antithrombotic drugs were not allowed within the treatment period but could be allowed thereafter in four trials ([Abe 1990](#); [EMS Bridging Trial](#); [Kikuchi 1994](#); [Mori 1992](#)). All patients received aspirin 300 mg starting 24 hours after randomisation in [Chen 2002](#). No antithrombotics were allowed in the first 24 hours in [Ducrocq 2005](#) or [DIAS 2005](#). [Sen 2008](#), [SYNTHESIS](#) and [SYNTHESIS EXPANSION](#) mentioned the use a variable amount of intra-arterial heparin either as a bolus ([SYNTHESIS](#); [SYNTHESIS EXPANSION](#)) or through heparinised flush solution during the interventional treatment ([Sen 2008](#)).

Eight trials used the 'overall neurological improvement rating' and side effects as their main outcome measures. Four of the trials assessed 'utility' (as judged by the neurological improvement and side effects). The others used standard stroke outcome measures: modified Rankin scale (mRS), European Stroke Scale (ESS), Barthel Index (BI). The number of patients who died, or had an intra or extracranial haemorrhage, could be extracted from all trials except one ([Kikuchi 1994](#)) in which extracranial haemorrhage was not reported. Seven trials mentioned activities of daily living (ADL) as part of their overall improvement measure, but most only reported the number of patients with improvements in the ADL score compared with their baseline score. Thus, we were not able to extract the number of dependent patients except from [Chen 2002](#), the [EMS Bridging Trial](#) and [Mori 1992](#), which used the BI and mRS to measure functional outcome. [Sen 2008](#) only describes neurological improvement at three months (defined as reduction in the National Institutes of Health Stroke Scale (NIHSS) score by four or more points) and it was not possible to extract the number of dependent patients at the end of follow-up.

Dependency was differently defined and followed up. [Kikuchi 1994](#) measured the BI at one month after the stroke, but only reported the mean BI for the two treatment groups, not the actual number of dependent patients. [Chen 2002](#) used a BI less than 95 and a mRS greater than 1, and the [EMS Bridging Trial](#) published details of individual patients' mRS. [SYNTHESIS](#) and [SYNTHESIS EXPANSION](#) defined good clinical outcome as mRS of 0 or 1. Where available, we

defined death or dependency at the end of follow-up as mRS 3 to 6 at the latest time interval available.

The duration of follow-up was only one month in eight trials and three months in 12 trials. The one-month functional outcome might not be relevant to the final true outcome because of insufficient time to allow maximum recovery.

Effects of interventions

This results section is split into three parts. The first part deals with direct comparisons of different doses of the same drug, the second part with direct comparisons of different drugs, and the third part with direct comparisons of different routes of administration of the same drug. It was not always possible to assess for statistically significant heterogeneity because of a paucity of trials, but where it was possible to test, none of the outcomes showed any statistically significant heterogeneity.

1. Comparison of higher dose with lower dose of the same drug

(a) Death or dependency at the end of follow-up

Seven trials (Chen 2002; DEDAS; DIAS-2; DIAS 2005; Mori 1992; Parsons 2012; TNK-S2B) provided this outcome (at three months after the stroke, apart from Mori 1992 where the follow-up was one month) and no statistically significant difference was observed between the higher dose and lower dose groups (OR 0.86, 95% CI 0.62 to 1.19, $I^2 = 27\%$) (Analysis 1.1). Kikuchi 1994 measured the BI and found no statistically significant difference in the mean BI score between the 20 and the 30 MIU treatment groups (mean BI score 46 versus 49 respectively, $P = 0.8$).

(b) Death (early and late)

Data for this outcome were available in 10 and 12 trials respectively regarding early (Analysis 1.2) and late deaths (Analysis 1.3). There was no statistically significant difference between the higher and lower-dose groups in terms of early (OR 1.09, 95% CI 0.66 to 1.80) or total deaths by the end of follow-up (OR 1.22, 95% CI 0.82 to 1.80, $I^2 = 32\%$). In patients allocated to the higher versus lower dose of desmoteplase, there were significantly more deaths at the end of the follow-up (OR 3.21, 95% CI 1.23 to 8.39).

(c) 'Significant' and fatal intracranial haemorrhage

All 13 trials provide data on 'significant' intracranial haemorrhage (Analysis 1.4) and 10 on fatal haemorrhages (Analysis 1.5). Kikuchi 1994 provides only the number of non-fatal intracranial haemorrhages but not the total symptomatic intracranial haemorrhages within the first two weeks. The definition of 'significant' haemorrhage is not always clear or standardised across the studies. Some trials define symptomatic intracranial haemorrhage (DEDAS; DIAS-2; DIAS 2005) as intracranial haemorrhage within 72 hours of treatment that led to an increase by four points or more in the NIHSS score. Others (TNK-S2B) define symptomatic haemorrhage as any haemorrhage seen on a follow-up CT that can explain any neurological worsening (appearance of new deficit or worsening of previous deficit persisting more than eight hours). Some trials (Chen 2002; Kikuchi 1994; Ohtomo 1985; Ohtomo 1988a; Ohtomo 1988b) did not clearly describe the relationship between clinical deterioration and the CT-confirmed intracranial haemorrhages, but they classified the severity of intracranial haemorrhage as mild, moderate and severe

(also not clearly defined). For those studies we collected the number of moderate or worse (or massive or mass effect on CT) as 'significant intracranial haemorrhages'. There were more significant intracranial haemorrhages in the patients allocated to higher doses than lower doses (OR 1.43, 95% CI 0.81 to 2.52, $I^2 = 0\%$), but the difference was not statistically significant. There were significantly more fatal intracranial haemorrhages in the high-dose group at the end of follow-up (OR 2.71, 95% CI 1.22 to 6.04, $I^2 = 0\%$) although the confidence intervals were wide because of the small number of events. If confirmed in future large trials, this would be equivalent to 23 more fatal intracranial haemorrhages per 1000 patients treated with high versus low-dose thrombolytic drugs. Despite the failure of some trials to define intracranial haemorrhage in terms of its clinical effect, it was possible to identify important relationships. For example, in Kikuchi 1994, eight of the 13 patients in the group treated with 30 MIU rt-PA who died were said to have 'cerebral haemorrhage with mass effect' or 'massive cerebral haemorrhage' compared with only one of the 13 patients in the group treated with 20 MIU rt-PA.

(d) Major extracranial haemorrhage

Nine trials provided these data (Analysis 1.6). There were more major extracranial haemorrhages in the patients allocated to the higher than the lower dose (OR 1.72, 95% CI 0.93 to 3.21) but the difference was not statistically significant.

2. Comparison of one drug with another

Five trials compared one agent with another - one trial of rt-PA versus UK (Abe 1990), one trial of t-PA versus UK (Ohtomo 1988b), one trial of tissue-cultured UK versus UK (Ohtomo 1985) and two trials of different doses of tenecteplase versus rt-PA (Parsons 2012; TNK-S2B). With the limitations described above, we included two trials (Parsons 2012; TNK-S2B) in this section comparing the cumulative outcome from two different doses of tenecteplase versus t-PA.

(a) Death or dependency at the end of follow-up

Only the tenecteplase trials contribute to this outcome. There was no significant difference in death or dependency at the end of follow-up between tenecteplase and t-PA (OR 0.58, 95% CI 0.31 to 1.09) (Analysis 2.1).

(b) Death

All trials reported the number of patients who died and the cause. There was no statistically significant difference in the number of deaths between patients treated with UK and another agent within the first two weeks (tissue-cultured UK versus UK, OR 1.37, 95% CI 0.23 to 8.09; rt-PA versus UK, OR 0.90, 95% CI 0.27 to 2.98). The tenecteplase trials did not provide this outcome (Analysis 2.2). There were slightly more deaths by the end of follow-up (Analysis 2.3) in the patients allocated to tissue-cultured UK-treated then in those allocated to UK (OR 1.81, 95% CI 0.36, to 9.19) and slightly fewer deaths in those allocated to rt-PA than in those allocated to UK (OR 0.72, 95% CI 0.26 to 2.02), but neither comparison was statistically significant. There was a tendency for fewer deaths at the end of follow-up in those allocated to tenecteplase versus those allocated to rt-PA, but this did not reach statistical significance (OR 0.52, 95% CI 0.21 to 1.27).

(c) 'Significant' and fatal intracranial haemorrhage (the heading 'significant' has been retained for consistency)

This outcome was available in all trials with the exception of the [TNK-S2B](#) trial where the number of fatal intracranial haemorrhages could not be extracted from the published data. There was a trend to fewer symptomatic intracranial haemorrhages within the first two weeks in the patients allocated to tissue-cultured UK or rt-PA than in those allocated to conventional UK but there were few events (one versus zero and one versus six haemorrhages respectively) and the difference was not statistically significant (OR 0.12, 95% CI 0.0 to 6.21; OR 0.26, 95% CI 0.06 to 1.18 respectively) ([Analysis 2.4](#)). Similarly, there was no significant difference in significant intracranial haemorrhage between those allocated tenecteplase or t-PA (OR 0.74, 95% CI 0.20 to 2.76). There were no fatal haemorrhages in the tissue-cultured UK versus UK comparison and only one fatal intracranial haemorrhage during the whole study period in the UK versus rt-PA comparison (OR 7.91, 95% CI 0.16 to 399.54) and only two fatal intracerebral haemorrhages in the TNK versus rt-PA comparison in one tenecteplase trial ([Parsons 2012](#); OR 0.47, 95% CI 0.02 to 9.02) ([Analysis 2.5](#)).

(d) Major extracranial haemorrhage

There were no major extracranial haemorrhages in the tissue-cultured UK versus UK comparison ([Analysis 2.6](#)). Only one non-fatal event occurred in each group in the UK versus rt-PA comparison (OR 1.07, 95% CI 0.07 to 17.17). There was one major extracranial non-fatal haemorrhage in the tenecteplase group versus none in the rt-PA group in the [TNK-S2B](#) trial (OR 3.99, 95% CI 0.05 to 318.43) but extracranial haemorrhage was not reported in [Parsons 2012](#). No fatal events occurred.

3. Comparison of different routes of administration of the same drug

There are five studies in this category, four comparing intravenous versus intra-arterial rt-PA ([EMS Bridging Trial](#); [Sen 2008](#); [SYNTHESIS](#); [SYNTHESIS EXPANSION](#)) and one comparing intravenous versus intra-arterial UK ([Ducrocq 2005](#)). Only one trial compares a combination of intravenous rt-PA plus intra-arterial rt-PA with intravenous placebo plus intra-arterial rt-PA ([EMS Bridging Trial](#)). The [EMS Bridging Trial](#) only included 35 patients and had an imbalance in baseline stroke severity which did not reach conventional statistical significance but which may, none the less, have influenced the outcomes in the two treatment arms in favour of intravenous placebo plus intra-arterial rt-PA. [Ducrocq 2005](#) is a single-centre, randomised trial comparing intravenous versus intra-arterial urokinase: 900,000 units of UK were given within six hours of stroke onset to 27 patients intravenously or intra-arterially (or less in the intra-arterial group if recanalisation had been achieved). The study was terminated early due to a high mortality rate. [Sen 2008](#) performed a feasibility study comparing intravenous (N = 4) versus intra-arterial (N = 3) t-PA in patients with acute ischaemic stroke who could start treatment within three hours of symptom onset and had evidence of major arterial occlusion on CT angiogram. [SYNTHESIS](#) was another pilot study evaluating intra-arterial t-PA up to six hours (N = 25 patients randomised, 19 treated) versus intravenous t-PA up to three hours (N = 29 patients randomised, 28 treated). Mechanical thrombus disruption or clot retrieval was allowed (used in 8/19 patients) but not balloon angioplasty. [SYNTHESIS EXPANSION](#) was a larger trial of intravenous (N = 181) versus intra-arterial (N = 181) rt-PA up to

4.5 hours after ischaemic stroke. Mechanical devices were allowed in addition to intra-arterial rt-PA and were used in 56/181 patients.

(a) Death or dependency at the end of follow-up

Four trials provided these data ([Ducrocq 2005](#); [EMS Bridging Trial](#); [SYNTHESIS](#); [SYNTHESIS EXPANSION](#)). The fifth study ([Sen 2008](#)) only describes neurological improvement at three months (defined as reduction in the NIHSS score by four or more points). There was no difference in the number of patients who were dead or dependent between those allocated intra-arterial thrombolysis (combined OR 1.08, 95% CI 0.15 to 1.55). The addition of the recently completed [SYNTHESIS EXPANSION](#) trial has increased the available data four fold - although the numbers are still small there is little evidence of any benefit of intra-arterial over intravenous therapy ([Analysis 3.1](#)).

(b) Death

There were no significant differences in the number of patients who died within the first two weeks between the two groups (OR 0.96, 95% CI 0.51 to 1.79) ([Analysis 3.2](#)). Similarly, at the end of follow-up, there was no significant difference in the number of patients who had died between the two treatment groups (OR 0.81, 95% CI 0.47 to 1.39) ([Analysis 3.3](#)).

(c) Symptomatic and fatal intracranial haemorrhage

All five studies provided data on symptomatic and fatal intracranial haemorrhage. The number of incidents is small and the confidence intervals are wide. There was no statistically significant difference between the patients allocated intra-arterial or intravenous treatment in the number of symptomatic (OR 1.10, 95% CI 0.4 to 2.25) ([Analysis 3.4](#)) or fatal intracranial haemorrhages (OR 0.67, 95% CI 0.21 to 2.11) ([Analysis 3.5](#)).

(d) Major extracranial haemorrhage

Only two studies ([SYNTHESIS](#); [SYNTHESIS EXPANSION](#)) gave details on extracranial haemorrhages describing 4/210 cases with extracranial haemorrhage in those allocated to intravenous therapy and 4/206 patients with groin haematomas two of which required surgical excision in those allocated to intra-arterial therapy.

DISCUSSION

The data from trials comparing different doses of the same thrombolytic agent, two different agents or two routes of administration are limited to only 2527 patients. In contrast to the evidence on thrombolytic therapy versus control, where more than 9000 patients have been randomised to thrombolysis or control ([Wardlaw 2009](#); [Wardlaw 2010](#)) and more than 6000 between rt-PA and control alone ([Wardlaw 2012](#)), the number of included patients in the group and subgroup analysis of this companion thrombolysis review is very small. Therefore, regrettably, we are not able to report any results that will have any significant impact on everyday clinical practice. The new studies included in this update are mainly 'dose ranging' studies evaluating new thrombolytic agents such as desmoteplase and tenecteplase, or 'pilot' or larger interventional studies comparing intravenous thrombolysis versus intra-arterial treatment, and therefore are very limited in their conclusions.

Two ongoing trials are comparing intra-arterial with intravenous thrombolysis ([BASICS](#); [ITAIS](#)). There is one other completed but unpublished trial ([FRALYSE](#)). The amount of data on intravenous

versus intra-arterial therapy increased four-fold from 123 to 485 patients with the publication of [SYNTHESIS EXPANSION](#). Other ongoing trials are comparing different doses of rt-PA (e.g. [ENCHANTED](#)) and should complete in the next five years.

On the early trials of this review there was little evidence on functional outcome - most of these trials did not collect such data, and two that did measure the BI ([Kikuchi 1994](#); [Mori 1992](#)) did it at only one month after the stroke, at which stage patients may still be improving. On a positive note, the published data in the last decade seem now to be more standardised when compared with earlier studies and typically contain basic information on baseline stroke characteristics and 90-day mRS. Hopefully this will bear fruit in future years as larger, better conducted and reported studies become available, enabling more meaningful comparisons and meta-analyses.

Many of the early trials used somewhat unconventional dosing regimens, such as a once daily dose for seven days, and may have started treatment up to several days after the stroke, so it is difficult to extrapolate these results to the sort of dosing regimens used in the recent trials comparing thrombolysis with placebo ([Wardlaw 2009](#); [Wardlaw 2010](#)). However, most of these early trials do not provide functional outcome data, therefore data on functional outcome come from recent trials (e.g. [EMS Bridging Trial](#); [Parsons 2012](#)) testing more conventional dosing regimens.

However, these limited data do suggest that there is some evidence that lower doses of thrombolytic agents cause fewer fatal (statistically significant) and 'clinically significant' (not statistically significant) intracranial haemorrhages. But there was no effect on the number of early deaths or total deaths at the end of follow-up, or the death and disability outcome at the end of the follow-up (and too few extracranial haemorrhages to make any comments). In the desmoteplase subgroup, there were significantly fewer deaths in the lower-dose than the high-dose subgroup.

The data on the comparison of different thrombolytic agents (rt-PA, t-PA, tissue-cultured UK, UK and tenecteplase) are extremely limited, with too few patients and outcome events to make any useful conclusions. There are no data comparing the dose of SK or of SK with other thrombolytic drugs. Desmoteplase and tenecteplase are variants of the native t-PA with theoretically improved pharmacokinetic properties. The prematurely terminated [TNK-S2B](#) trial included a subgroup (N = 31) of patients that received t-PA; too small to draw any conclusions. [Parsons 2012](#) had 25 patients randomised to rt-PA and only 50 to two different doses of TNK, again rather too small for reliable conclusions.

Recently there has been an emerging interest in the use of interventional devices to treat acute stroke (mechanical devices alone or in addition to pharmacological therapy) and many centres in developed countries worldwide offer intra-arterial thrombolysis/thrombectomy for stroke due to large vessel occlusion ([RECANALISE 2009](#)). This interest is often based on concepts such as that intra-arterial therapy or mechanical devices, or both, increase recanalisation rates, or are safer because they use lower doses of thrombolytic drug ([Cicone 2007](#)). Until the publication of [SYNTHESIS EXPANSION](#) and [IMS-III](#), the use of interventional mechanical devices was based on very limited evidence, mostly registries or case series and virtually none of it randomised ([Galimanis 2012](#)). [IMS-111](#) showed no

benefit for mechanical intra-arterial devices over intravenous rt-PA, which taken together with the data in [Analysis 3.1](#) shows no benefit for intra-arterial/interventional mechanical devices over intravenous rt-PA. There is also increasing interest in the use of adjunctive methods to enhance pharmacological or spontaneous thrombolysis, for example using transcranial ultrasound ([Tsivgoulis 2010](#)). At the outset of this update we were interested in evaluating the different interventional techniques and devices. However, it soon became clear that this would be premature as there are no randomised studies comparing the various interventional procedures. It was therefore more important to establish whether intra-arterial treatment works in the first place and if it offers any particular advantage over intravenous treatment. The four randomised studies of intravenous versus intra-arterial treatment that have been conducted so far were small (123 patients in total) and too heterogeneous to draw any definitive conclusions. Differences in stroke severity, intra-arterial techniques, dose and technique of thrombolytic administration, use of mechanical devices, variable doses of heparin, difficulties of blinding and subsequent follow-up assessment are only a few of the factors that may introduce significant bias in these small studies. This review indicates that intra-arterial therapy confers no benefit over intravenous therapy either in terms of reduced dependency or death or reduced haemorrhage. At present, intravenous rt-PA remains best practice and intra-arterial therapy or mechanical devices should only be used in randomised trials or in exceptional situations.

Two trials ([Chen 2002](#); [Kikuchi 1994](#)) contributed most of the data on significant intracranial haemorrhage, yet there were problems in the definition of the intracranial haemorrhage - the authors graded the severity of the haemorrhage on the CT brain scan appearance, not on whether the haemorrhage was associated with clinical deterioration or death. [Chen 2002](#) used the term 'symptomatic intracranial haemorrhage' without an exact definition. Therefore, in some analyses we have adopted the term 'significant intracerebral haemorrhage' to take account of this. It was possible to extract the number of patients dying with mass effect (on CT brain scan), or 'massive intracranial haemorrhage' where the authors appeared to have attributed the cause of death to the haemorrhage, but nevertheless these data must be regarded with extreme caution. The patients who died of neurological causes but did not have brain imaging or autopsy may have had fatal intracranial haemorrhage, therefore the total number of deaths within the first two weeks (most likely to be of neurological causes) is a more reliable end point than fatal intracranial haemorrhage because of these definition problems.

Thus more, larger trials are needed to answer questions on which drug, or dose of thrombolysis and if there are any situations when intra-arterial thrombolysis with or without mechanical clot removing devices might be best, including collecting data on functional outcome as well as deaths, and intra and extracranial haemorrhages, clearly defined in terms of their clinical effect.

AUTHORS' CONCLUSIONS

Implications for practice

The data provide limited evidence that higher doses of thrombolytic drugs lead to higher rates of fatal intracranial haemorrhage. Apart from that, the data are insufficient to answer questions about which drug or dose might be best for thrombolysis.

That is not to say that one drug might be better (or worse) than others, but simply that the randomised evidence does not exist. Data on route of administration are more substantial and do not support routine use of intra-arterial therapy over intravenous therapy. At present intravenous rtPA as licensed should be regarded as best practice. Please refer to the Cochrane review of 'Thrombolysis for acute ischaemic stroke' (Wardlaw 2009) for conclusions on the broader question of the use of any thrombolytic agent, and of rt-PA specifically (Wardlaw 2012), in acute ischaemic stroke.

Implications for research

More, larger randomised controlled trials are required to answer questions about which drug, or dose is best for thrombolysis, and whether there are any situations in which intra-arterial therapy with or without a mechanical clot extracting device is better than intravenous rt-PA. Such trials should collect data on functional outcome assessed using the modified Rankin Scale or Barthel Index at a minimum of three months after the stroke, and should clearly define intracranial haemorrhage in terms of its clinical effects (for example 'asymptomatic', 'symptomatic' or 'fatal'). Patients dying of neurological causes without immediate prior brain imaging should, wherever possible, undergo autopsy examination.

There are no randomised comparisons of streptokinase with rt-PA or urokinase, only of rt-PA with urokinase or tenecteplase. Larger

randomised trials are required to evaluate the newer thrombolytic agents such as desmoteplase and tenecteplase and compare them to the widely used rt-PA. Future trials also need to address whether interventional management of stroke offers any particular advantage and in which group of patients. Future trials could usefully address these areas to try to find ways of reducing the risk (and improving the chance of benefit) with thrombolysis.

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If you are aware of any additional trials, please let us know.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abe 1981

Methods	Sequentially numbered identical containers Blinding: double Lost to follow-up: 1 in high-dose group, 5 in control group
Participants	Japan 101 patients 71% < 70 years, 61% male Cerebral thrombosis 100% pre-entry CT (probably) Time since stroke: < 2 weeks Comparability of groups: age, sex, severity similar
Interventions	Higher dose: UK (manufactured by Green Cross, Japan) 60 000 U/day intravenously over 1 hour for 7 days Lower dose: UK 6000 U/day intravenously over 1 hour for 7 days Antithrombotic drugs were not allowed within the 7 days of treatment period, but could be used thereafter
Outcomes	Overall improvement rating at 1 week and 4 weeks after treatment start Death Intracranial haemorrhage Extracranial haemorrhage Utility
Notes	Exclusion criteria: embolic stroke, severe strokes, bleeding tendency Follow-up: 1 month

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequentially numbered envelopes
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Abe 1981 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal
Selective reporting (reporting bias)	Unclear risk	Not stated

Abe 1990

Methods	Sequentially numbered identical containers Blinding: double Lost to follow-up: 1 in treatment group, 1 in control group
Participants	Japan 230 patients in total (71 versus 76 for higher dose versus lower dose, 71 versus 83 for rt-PA versus UK) 63% < 70 years, 66% male Cerebral thrombosis 100% pre-entry CT Time since stroke: < 3 days in most Comparability of groups: age, sex, severity similar, more hypertension and diabetes in control group, more heart disease in treatment group
Interventions	Higher dose (rt-PA): rt-PA (SM-9527) 2 MU/day intravenously over 1 hour for 7 days Lower dose (rt-PA): rt-PA (SM-9527) 1 MU/day intravenously over 1 hour for 7 days UK group: UK 60,000 IU/day intravenously over 1 hour for 7 days Antithrombotic drugs were not allowed all the time, but could have exception
Outcomes	Global improvement rating in 3 days, 1, 2 and 4 weeks Activity of daily living Death Intracranial haemorrhage Extracranial haemorrhage ELT, plasma FDP, fibrinogen, plasminogen and a2-plasmin inhibitor
Notes	Exclusion criteria: embolic stroke, bleeding tendency, severe strokes Follow-up: 4 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequentially numbered envelopes
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Abe 1990 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Minimal losses

Atarashi 1985

Methods	Sequentially numbered identical containers Blinding: double Lost to follow-up: 4 in low-dose group
Participants	Japan 195 patients 64% < 70 years, 72% male Cerebral thrombosis 100% pre-entry CT Time since stroke: 5 days Comparability of groups: age, sex, severity similar
Interventions	Higher dose UK 240,000 U/day intravenously over 3 hours for 7 days Lower dose UK 60,000 U/day intravenously over 3 hours for 7 days Placebo group Antithrombotic drugs were not allowed all the time, but could have exception
Outcomes	Final global improvement rating Utility Activity of daily living Death Intracranial haemorrhage Extracranial haemorrhage Plasma fibrinogen and FDP levels
Notes	Exclusion criteria: embolic stroke, ICH, severe strokes Follow-up: 4 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequentially numbered envelopes
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke (Review)

Atarashi 1985 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses

Chen 2002

Methods	Randomisation numbers Blind: double Intention-to-treat
Participants	China (51 hospitals) 511 patients. 35 to 75 years. 347 for comparison of different doses
Interventions	In 170 patients: UK 1.5 mμ intravenously In 177 patients: UK 1.0 mμ intravenously In 164 patients: placebo (saline) within 6 hours of stroke onset
Outcomes	ESS day 1, 3, 7 and 30, BI, mRS at 90 days, symptomatic ICH, mortality, extracranial haemorrhage
Notes	Exclusion criteria: < 35 or > 75 years, comatose, > 3 muscle weakness. All received aspirin starting at 24 hours post randomisation. Heparin not specifically mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method unclear - sounds like sequential numbers
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	

DEDAS

Methods	Multicentre, double-blind, randomised, placebo-controlled, dose-escalation study of desmoteplase at 3 to 9 hours post stroke: phase II study Interactive voice response randomisation system, no stratification
Participants	Multicentre trial (US and Germany) March 2003 to October 2004 3 to 9 hours post stroke onset with > 20% perfusion/diffusion mismatch NIHSS 4 to 20 Isolated ICA occlusion without coexisting separate MCA occlusion excluded due to difficulty distinguishing acute from chronic ICA occlusion
Interventions	Participants randomised to desmoteplase 90 µg/kg (N = 14) versus 125 µg/kg (N = 15) versus placebo (N = 8)
Outcomes	Symptomatic ICH, death, anaphylaxis, major systemic bleeding Reperfusion at 4 to 8 hours post treatment Clinical outcome at 90 days
Notes	MRI performed at presentation, 4 to 8 hours after treatment and at 30 days. CT at 24 hours 12 protocol violations (6 had no mismatch, 6 had isolated ICA occlusion) Baseline DWI lesion volumes (larger in placebo) and baseline NIHSS (highest in placebo) not balanced Anticoagulants or antiplatelets not allowed first 24 hours

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	

DEDAS (Continued)

Selective reporting (re-reporting bias)	Low risk
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DIAS 2005

Methods	Placebo-controlled, double-blind, randomised, multicentre phase II trial Randomisation by interactive voice response system, no stratification
Participants	Patients with acute stroke, 3 to 9 hours from onset with > 20% perfusion diffusion mismatch on MRI 44 centres in 12 countries between January 2001 and October 2003
Interventions	Dose finding study. Intravenous desmoteplase bolus over 1 to 2 minutes Part 1: 25 mg (N = 17) versus 37.5/50 mg (N = 13) versus placebo (N = 16) Part 1 stopped due to high symptomatic ICH rate (8/30) Part 2 : 62.5 µg/kg (N = 15) versus 90 µg/kg (N = 15) versus 125 µg/kg (N = 15) versus placebo (N = 11)
Outcomes	Rate of symptomatic ICH, major systemic bleeding, anaphylaxis, death mRS, BI, NIHSS at 90 days Reperfusion at 4 to 8 hours post treatment, change in infarct volume at 30 days
Notes	MRI at screening, 4 to 8 hours post-treatment and 30 days Anticoagulants and antiplatelets not allowed in the first 24 hours 37.5 mg and 50 mg due to the low numbers were analysed together In the data analysis in this review only the doses 125 µg/kg versus 90 µg/kg have been included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

DIAS-2

Methods	Randomised, placebo-controlled, double-blind, dose ranging study phase III study Testing the effect of 2 doses of desmoteplase at 3 to 9 hours post stroke Computer-generated randomisation codes, stratified by centre, double-blinded
Participants	Multicentre trial (Europe, North America, Australia, China) June 2005 to March 2007 3 to 9 hour post onset with > 20% potentially salvageable tissue as defined by perfusion study (CT or MR) 18 to 85 years old, NIHSS 4 to 24
Interventions	Participants randomised to 90 µg/kg (N = 57) or 125 µg/kg (N = 66) of desmoteplase or placebo (N = 63) 1 intravenous bolus over 1 to 2 minutes
Outcomes	Good clinical outcome at 90 days = improvement in NIHSS > 8 points and BI 75 to 100 and mRS 0 to 2 Intracranial haemorrhage (symptomatic or asymptomatic), major haemorrhagic event, death Change in infarct volume between baseline and 30 days
Notes	Baseline study and follow-up by same modality at 30 days. CT at 24 to 72 hours to assess for haemorrhage Less severe strokes than DIAS 2005 / DEDAS studies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	

Ducrocq 2005

Methods	Single-centre, randomised study comparing intravenous versus intra-arterial UK
Participants	27 patients, France Stroke onset < 6 hours. Hypodensity in > 1/3 of the MCA not an exclusion criterion
Interventions	900,000 IU intravenous (N = 14) versus 900,000 units intra-arterially (N = 13) Intravenous group: 300,000 IU bolus over 10 minutes, 600,000 IU over 50 minutes Intra-arterial group pulsed spray injections, 20,000 IU per minute up to 900,000 in 45 minutes or until complete recanalisation
Outcomes	Number of patients with mRS 0 to 2 at 90 days Death in first 90 days Symptomatic intracranial haemorrhage (fatal or not) Scandinavian Score Scale at 7, 30, 90 days BI at 90 days
Notes	December 1995 to August 1997 Prematurely terminated due to high mortality rate No diagnostic procedure to determine the presence of vessel occlusion in the intravenous group Treatment in the intra-arterial group began significantly later than the intravenous group (mean of 68 minutes). 1 protocol violation in the intra-arterial group No heparin or aspirin in the first 24 hours Method of randomisation not described Evaluation by investigator not blinded to the treatment allocation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method unclear
Allocation concealment (selection bias)	Unclear risk	Method unclear
Blinding (performance bias and detection bias) All outcomes	High risk	Single-centre; not blinded
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-centre; not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-centre; not blinded

Ducrocq 2005 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses unclear
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EMS Bridging Trial

Methods	Randomisation - stratified block scheme by clinical centre Double-blind, placebo-controlled, intention-to-treat
Participants	USA, multicentre 35 patients Upper age 84 years; within 3 hours of CT proven ischaemic stroke; NIHSS > 5
Interventions	(1) Intravenous rt-PA (0.6 mg/kg, 60 mg maximum, 10% as bolus over 1 minute and the rest over 30 minutes) followed immediately by angiography and intra-arterial rt-PA if clot seen - 1 mg beyond the thrombus, 1 mg into the thrombus then 10 mg/hour infused for 2 hours maximum (2) Intravenous placebo matched in appearance to rt-PA followed by intra-arterial rt-PA as in group 1. Amount of intra-arterial rt-PA and duration of intra-arterial infusion not given
Outcomes	7-point or more improvement on the NIHSS by 7 to 10 days or NIHSS 0 or 1 at 7 days; life-threatening bleeding; mRS, Barthel, GOS at 90 days; arterial patency at 2 hours as measured with the TIMI scale
Notes	Done from February 1995 to March 1996. No heparin or aspirin within 24 hours

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	Double-blind elements
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Some elements blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses

Kikuchi 1994

Methods	Sequentially numbered identical containers Blinding: double Lost to follow-up: 1 in treatment group, 1 in control group
Participants	Japan 132 patients 74% < 70 years, 58% male Cerebral embolism 100% pre-entry CT Time since stroke: < 6 hours Comparability of groups: age, sex, severity and associated diseases similar
Interventions	Higher dose rt-PA (duteplase, SM 9527) 30 MIU intravenous infusion for 1 hour Lower dose rt-PA (duteplase, SM 9527) 20 MIU intravenous infusion for 1 hour Drugs which might have interactions with thrombolysis were not allowed within 7 days of treatment period, but could be used thereafter
Outcomes	Neurological impairment scale at 4 weeks Disability (BI) at 4 weeks Global improvement rating scale Death Intracranial haemorrhage
Notes	Exclusion criteria: severe stroke, bleeding tendency, pregnancy, severe high blood pressure Follow-up: 4 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses
Selective reporting (reporting bias)	Low risk	

Mori 1992

Methods	Sequentially numbered identical containers Blinding: double Lost to follow-up: 0
Participants	Japan 19 patients Mean age 67 years, 53% male Thromboembolic stroke in internal carotid artery territory 100% pre-entry CT and angiography Time since stroke: < 6 hours Comparability of groups: age, associated diseases similar, more males in the lower dose group (78% versus 30%)
Interventions	Higher dose rt-PA (duteplase supplied by Sumitomo Pharmaceuticals, Tokyo) 30 MIU (60 mg) intra-venous infusion for 1 hour Lower dose rt-PA (duteplase) 20 MIU (40 mg) intravenous infusion for 1 hour Placebo group Antithrombotic drugs were not allowed within 24 hours after infusion, but could be allowed thereafter
Outcomes	Angiographic recanalisation Death Neurological improvement Intracranial haemorrhage Extracranial haemorrhage BI at 1 month
Notes	Exclusion criteria: pre-entry CT abnormality related to ischaemic events, > 80 years, severe strokes, bleeding tendency Follow-up: 1 month

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central telephone randomisation
Allocation concealment (selection bias)	High risk	Double-blind
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses

Mori 1992 (Continued)

Selective reporting (re-reporting bias)	Unclear risk	Unclear
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Ohtomo 1985

Methods	Sequentially numbered identical containers Blinding: double Lost to follow-up: 1 in UK group
Participants	Japan 170 patients 58% < 70 years, 64% male Cerebral thrombosis 100% pre-entry CT Time since stroke: < 5 days Comparability of groups: age, sex, severity similar
Interventions	UK: 60,000 U/day intravenously over 1 hour for 7 days T-UK: 60,000 U/day intravenously over 1 hour for 7 days Antithrombotic drugs were not allowed all the time, but could have exception
Outcomes	Symptoms and signs General improvement Utility Death Intracranial haemorrhage Extracranial haemorrhage Activity of daily living
Notes	Exclusion criteria: embolic stroke, ICH, severe strokes, bleeding tendency Follow-up: 4 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Double-blind
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Ohtomo 1985 (Continued)

Incomplete outcome data (attrition bias)	Low risk	Minimal losses
All outcomes		

Ohtomo 1988a

Methods	Sequentially numbered identical containers Blinding: double Lost to follow-up: 2 in treatment group, 4 in control group
Participants	Japan 131 patients 64% < 70 years, 65% male Cerebral thrombolysis 100% pre-entry CT Time since stroke: < 3 days Comparability of groups: age, severity similar, more male in the control group (76% versus 53%)
Interventions	Higher dose t-PA (AK-124) 60,000 U/day intravenously over 1 hour for 7 days Lower dose t-PA (AK-124) 36,000 U/day intravenously over 1 hour for 7 days Antithrombotic drugs were not allowed all the time, but could have exception
Outcomes	Symptoms and signs General improvement Death Intracranial haemorrhage Extracranial haemorrhage Utility Activity of daily living
Notes	Exclusion criteria: embolic stroke, haemorrhagic stroke, severe strokes, bleeding tendency Follow-up: 4 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Double-blind
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Ohtomo 1988a (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses
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Ohtomo 1988b

Methods	Sequentially numbered identical containers Blinding: double Lost to follow-up: 7 for 14 days, 2 for 4 weeks in t-PA group, 6 for 14 days, 7 for 4 weeks in UK group
Participants	Japan 364 patients 62% < 70 years, 66% male Cerebral thrombosis 100% pre-entry CT Time since stroke: < 3 days in most Comparability of groups: age, sex, severity similar
Interventions	t-PA: (AK-124) 36,000 AKU/day intravenously over 1 hour for 7 days UK: 60 000 IU/day intravenously over 1 hour for 7 days Antithrombotic drugs were not allowed all the time, but could have exception
Outcomes	Symptoms and signs General improvement Death Intracranial haemorrhage Extracranial haemorrhage Activity of daily living
Notes	Exclusion criteria: embolic stroke, unconsciousness, severe strokes, ICH, bleeding tendency Follow-up: 4 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Double-blind
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Ohtomo 1988b (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	More losses
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Parsons 2012

Methods	Acute ischaemic stroke patients with symptom onset < 6 hours randomised 1:1:1 to standard dose intravenous t-PA (0.9 mg/kg) or 0.1 mg/kg TNK or 0.25 TNK
Participants	Acute ischaemic stroke patients with symptom onset < 6 hours randomised into blocks of 15 patients. Recruitment completed with 75 patients randomised at 3 Australian University Hospitals
Interventions	Tenecteplase: given as a single intravenous bolus (over 1 minute), on one of 2 doses (0.1 mg/kg or 0.25 mg/kg) or alteplase: given intravenously 0.9 mg/kg, 10% as bolus (over 1 minute) and the remaining 90% as a 1-hour infusion immediately following the bolus
Outcomes	Blinded measurement extent of reperfusion of the MTT lesion at 24 hours
Notes	Abstract and trial database entry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method unclear
Allocation concealment (selection bias)	High risk	Central telephone randomisation but trial treatment given open-label; 3 centres; intensive baseline imaging; centralised image analysis; hard to blind clinical outcome assessors to allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Central image adjudication but unclear if follow-up images analysed separately from baseline; plus hard to blind effectively in a small data set
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dead patients not counted in primary outcome as did not undergo repeat imaging

Sen 2008

Methods	Feasibility study comparing intravenous versus intra-arterial rt-PA in acute ischaemic stroke with major vessel occlusion
	Computer-generated randomisation

Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke (Review)

Sen 2008 (Continued)

	Open-label study, blinded follow-up
Participants	<p>Single-centre study, North Carolina.</p> <p>< 3 hours from stroke onset</p> <p>NIHSS > 4</p> <p>Evidence of major vessel occlusion on CTA (M1/M2, ICA, VA/BA). Acute hypodensity > 1/3 of the MCA territory excluded</p>
Interventions	Intravenous t-PA (N = 4) 0.9 mg/kg as per NINDS protocol versus intra-arterial t-PA (N = 3) delivered by microcatheter 1 mg in thrombus, 1 mg beyond thrombus and the pulse spray method proximal to thrombus up to maximal dose of 20 mg or until TIMI 3 vessel patency
Outcomes	<p>Time to clinical/radiological assessment, time from eligibility to treatment</p> <p>Proportion of patients receiving timely assessments and treatment</p> <p>Symptomatic ICH at 24 hours, all haemorrhages within 90 days</p> <p>Reduction of NIHSS > 4 at 90 days</p> <p>Recanalisation on 24 hour MRA</p>
Notes	Consecutive patients presenting between October 2004 to December 2006 (7/9 eligible patients randomised)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported that computer-generated although minimisation, etc. not mentioned
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Reported that blinded outcome but difficult in single-centre study if open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Reported that blinded outcome but difficult in single-centre study if open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	Small study

SYNTHESIS

Methods	Open-label randomised controlled trial with blinded follow-up. Pilot study
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SYNTHESIS (Continued)

Random assignment by opaque envelopes, stratified per centre

Participants	Stroke of any ischaemic type, within 3 hours of onset, age over 18 years 4 Italian centres between January 2004 and February 2008
Interventions	intra-arterial rt-PA up to 6 hours (N = 25 patients randomised, 19 treated) versus intravenous rt-PA up to 3 hours (N = 29 patients randomised, 28 treated) Up to 0.9 mg/kg rt-PA (mean dose 50 mg (45 to 70 mg)) over 60 minutes intra-arterially into the thrombus within 6 hours versus 0.9 mg/kg (maximum 90 mg) over 60 minutes intravenously within 3 hours of onset (median time from stroke to onset of infusion 195 minutes for intra-arterial versus 155 minutes for intravenous) Mechanical thrombus disruption or clot retrieval were allowed (used in 8/19 patients) but not balloon angioplasty
Outcomes	7-day neurological deficit (NIHSS); CT at 2 to 4 days; 3 months survival free of disability (mRS 0 or 1), 3-month mRS assessment by telephone call
Notes	Aspirin to be avoided for first 24 hours. Intravenous heparin during angiography

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation but sealed envelopes
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Central blinded outcome assessment but open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported to be blinded follow-up; 4 centres
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few missing outcomes
Selective reporting (reporting bias)	Low risk	None evident

SYNTHESIS EXPANSION

Methods	Multicentre randomised trial
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SYNTHESIS EXPANSION (Continued)

Participants	Acute stroke patients able to initiate intravenous rt-PA within 3 hours and intra-arterial thrombolysis within 6 hours of stroke onset
Interventions	Intra-arterial alteplase and/or mechanical thrombectomy versus 0.9 mg/kg intravenous rt-PA; ia rt-PA alone used in 109/181 and rt-PA + device in 59 patients
Outcomes	mRS at 90 days, intracerebral haemorrhage, death
Notes	Recruitment completed 17 April 2012 with 362 patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	central simple randomisation system
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	90 day follow up done by central blinded assessor. early assessments may be biased by knowledge of treatment
Blinding of participants and personnel (performance bias) All outcomes	High risk	patients and operators unblind to IA v iv therapy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	central blinded assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	no loss to follow up
Selective reporting (reporting bias)	Low risk	no evidence of selective reporting

TNK-S2B

Methods	Multicentre, double-blind, randomised controlled trial, comparing 3 different doses of TNK versus rt-PA Web-based randomisation Phase IIb trial that was planned to continue with a phase III part but was prematurely terminated
Participants	USA, 8 centres, 112 patients, < 3 hours from stroke 2006 to 2008
Interventions	0.1 mg/kg TNK (N = 31) versus 0.25 mg/kg TNK (N = 31) versus 0.4 mg/kg TNK (N = 19) versus rt-PA (N = 31)
Outcomes	mRS at 90 days

Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke (Review)

TNK-S2B (Continued)

Symptomatic and asymptomatic ICH

Major systemic bleeding

Death within 90 days

Notes

March 2006 to December 2008

24-hour neurological status/symptomatic ICH used to define early the best dose of TNK

0.4 mg/kg dose 'dropped' early as inferior to the other 2

Prematurely terminated due to slow enrolment - 'post-specified' statistical analysis

Patients in the rt-PA group had more severe stroke

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web-based randomisation
Allocation concealment (selection bias)	Low risk	Double-blind, web-based
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses evident
Selective reporting (reporting bias)	Unclear risk	Stopped early

Wang 2003

Methods	Patients with acute cerebral infarction randomly allocated to 3 treatment groups, method of randomisation not described
Participants	Single-centre study, China
Interventions	rt-PA 0.9 mg/kg (N = 34) versus rt-PA 0.7 mg/kg (N = 33) versus no treatment
Outcomes	Clinical outcomes at 24 hours and 90 days: Chinese Stroke Scale and BI

Wang 2003 (Continued)

ICH and deaths

Notes	Number of dependent patients at 90 days or definition of dependency on the BI not given	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No details of randomisation methods
Allocation concealment (selection bias)	High risk	Method of randomisation not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	Unclear; single-centre study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unclear; single-centre study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unclear; single-centre study
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear

BI: Barthel Index
 C: concealment of allocation
 CT: computed tomography
 CTA: CT angiography
 DWI: diffusion-weighted imaging
 ELT: euglobulin clot lysis time
 ESS: European Stroke Scale
 FDP: fibrin degradation products
 GOS: Glasgow Outcome Scale
 ICA: internal carotid artery
 ICH: intracranial haemorrhage
 MCA: middle cerebral artery
 MRA: magnetic resonance angioplasty
 MRI: magnetic resonance imaging
 mRS: modified Rankin Scale
 MTT: mean transit time
 NIHSS: National Institutes of Neurological Disorders and Stroke Scale
 NINDS: National Institute of Neurological Disorders and Stroke
 rt-PA: recombinant t-PA
 TNK: tenecteplase
 t-PA: tissue plasminogen activator
 T-UK: tissue-cultured urokinase
 TIMI scale: Thrombolysis In Myocardial Infarction scale
 UK: urokinase
 Utility: effect judged from improvement and side effects

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

Study	Reason for exclusion
Abciximab 2001	Not a trial of a thrombolytic agent
Amaro 2007	Evaluates the effect of addition of uric acid to rt-PA as a neuroprotective agent
ARTIS	Evaluates the effect of intravenous aspirin in addition to rt-PA in acute stroke
Australian UK Trial	Randomised trial. Compares intra-arterial UK + anticoagulation versus anticoagulation alone in posterior circulation stroke. Excluded because it does not compare 2 direct thrombolytic agents
Brichta 2010	Abstract only. Dose range-finding stopped prematurely. Non-random, open-label study
Bu 1998	Patients treated early (within 3 hours) or late (about 12 hours) after acute ischaemic stroke but on the basis of time of admission so not actually randomised. Treatment was mannitol + intravenous UK + aspirin
CARNEROS-1	Dose-escalation study, not a randomised study. Company ended further clinical development of al-fimeprase
Christoforidis 2008	Not a randomised study. Retrospective angiographic evaluation of intra-arterial thrombolysis results depending on the technique of thrombolytic delivery
CLEAR-ER	Confounded by the use of eptifibatide
Davalos 2003	No longer relevant - trial never started
Del Zoppo 1989	This was the original Burrough's Wellcome dose range-finding study of t-PA. It was not randomised. Either 0.12, 0.20, 0.29 or 0.37 x 10,000,000 U/kg/60 minutes intravenous t-PA within 8 hours of ischaemic stroke. Follow-up was at 72 hours. The full results have never been published
Ding 2006	Relevant to Wardlaw 2009 . Testing aspirin + lumbrokinase versus aspirin alone after stroke
Dong 2003	Study comparing intra-arterial versus intravenous UK. Excluded because not a randomised study. Follow-up 2 weeks
Fan 2001	Antithrombosis enzyme (reptilase) versus dextran-40 for 10 days in acute ischaemic stroke. Not related to thrombolytic treatment dosology in hyperacute stroke
Gahn 2004	Compares rt-PA (0.9 mg/kg) versus rt-PA (0.45 mg/kg) + abciximab (0.125 mg/kg bolus + 12 hour infusion 0.125 micro g/kg x minute) in acute ischaemic stroke. Excluded because it is confounded by the use of abciximab and not randomised
Gao 1994	UK (40,000 UI for 7 days) intra-arterially into the carotid artery versus UK (40,000 UI for 7 days) intravenously. No data were given on functional outcome, only on blood count and ESR. 25 patients per group. The authors did comment that injection into the carotid artery had side effects while injection into a peripheral vein is easier, has less pain and complications. Excluded due to lack of relevant data
Geng 1998	Evaluates intra-arterial UK by DSA (20,000 to 40,000 units) versus intravenous UK (10,000 to 20,000 on day 1 then 20,000 to 40,000 for 4 days) in acute ischaemic stroke. Excluded because not a randomised study
Huang 1996	Evaluates intravenous venom (Svate-IV). Not a thrombolytic agent so not relevant to this the review

Study	Reason for exclusion
ICTUS-L	Not relevant to this review. Testing hypothermia as an adjunct to rt-PA
IMS I & II	Non-random comparison
IMS-III	RCT of mechanical device versus iv rt-PA, not ia v iv rt-PA
ITAIS-II	Non-randomised multicentre study of CT perfusion and angiography imaging in patients treated with rt-PA
Itoh 1998	Sodium ozagrel versus UK in patients with acute cerebral infarction in the territory of the internal carotid artery. Testing antiplatelet agent (ozagrel), not active thrombolysis. Not relevant to this review
J-ACT	Single-arm, non-randomised study testing 0.6 mg/kg of rt-PA
J-MARS 2010	Non-random registry of treated patients
Kim 2007	Intra-arterial tirofiban following intra-arterial UK versus intra-arterial UK alone in acute ischaemic stroke. Excluded because testing antiplatelet agent (tirofiban) as adjunct to intra-arterial UK versus UK alone
Kim 2008	Evaluates mechanical thrombolysis (MT) versus MT + intra-arterial t-PA (20 mg) versus MT + intra-arterial UK (300,000) in patients with MCA or ICA occlusion. Excluded because not a randomised study
Konta 1996	Abstract presented but no further information forthcoming. UK 240,000 IU day 1, 120,000 IU day 2, 60,000 IU day 3 versus UK 420,000 IU on day 1. 28 patients. Neurological outcome assessed at discharge. Stated that divided infusion produced "better" result than bolus but details not given
Lavallee 2007	Stent-assisted intra-arterial thrombolysis and/or thrombectomy versus intravenous thrombolysis (0.9 mg/kg) in patients with tandem internal carotid and MCA occlusion with ICA dissection. Excluded because not a randomised study
Lee 1994	Confounded by different time windows, e.g. intravenous UK versus intravenous heparin (begun within 12 hours of stroke onset) versus intra-arterial UK (begun within 6 hours of stroke onset)
Leker 2007	Not relevant to this review. t-PA (0.9 mg/kg infused over 1 hour) + aspirin (500 mg) versus t-PA alone in acute ischaemic stroke patients < 4.5 hours from onset
Li 2000f	Non-randomised
Li 2003b	Not testing thrombolysis dosology. Evaluating acupuncture versus UK
Li 2003e	Tongnao huoluo acupuncture versus UK (12 million units) versus placebo in acute ischaemic stroke (within 6 hours of onset). Not testing thrombolysis, evaluating acupuncture
Liu 1991a	Non-random. Confounded by dextran and other agents
Liu 2000b	Intravenous UK versus dextran from 2 to 12 hours after onset of stroke. Not relevant to this review
Luo 1997	Intra-arterial UK 100,000U every other day via carotid artery versus dextran (500 ml) in acute ischaemic stroke. Patients may also receive alylsantinfartase + venorutin. Not relevant to this review

Study	Reason for exclusion
Lyden 2003	Hypothermia + t-PA versus hypothermia versus t-PA versus control in acute ischaemic stroke patients 3 to 6 hours after stroke. Patients less than 3 hours from stroke onset will receive either t-PA or t-PA + hypothermia. Not relevant to this review
Lyden 2003a	Trial of hypothermia not thrombolysis
Macleod 2005	Randomised trial, evaluates the efficacy of intra-arterial UK versus control (no thrombolysis) in posterior circulation stroke. All patients received heparin/warfarin. Not relevant to this review
MELT	Trial of thrombolysis versus placebo - included in Wardlaw 2009
MITI-IV	Intravenous microplasmin (3 dose regimens) versus placebo in ischaemic stroke patients within 12 hours of onset; follow-up 90 days. This study was excluded because microplasmin has a very short half life and when given intravenously it does not have a direct thrombolytic effect
Morris 2003	Open-label phase 1 safety study. 3 dose tiers of intravenous rt-PA (0.45, 0.60 and 0.75 mg/kg) plus full-dose abciximab. 42 patients to be enrolled. Primary outcome intracranial haemorrhage. Started September 2002. Excluded because not randomised or blinded
Qiang 2001	Thrombolysis versus low-molecular-weight heparin (4100 IU subcutaneously 2 times per day) in patients within 6 hours of acute ischaemic stroke; follow-up 7 days. Not testing two thrombolytic agents
Qureshi 2002	Excluded because non-random dose-escalation study of reteplase in the presence of abciximab
Qureshi 2006	Comparison of 4 doses of intra-arterial reteplase (0.5, 1, 1.5 and 2 units) in acute ischaemic stroke (3 to 6 hours after onset). All patients received intravenous abciximab. Excluded because not a randomised study and also confounded by the use of abciximab
ReoPro Retavase MRI	Excluded because non-random dose-escalation study of reteplase in the presence of abciximab
Riedel 1996	Study was terminated because of recruitment problems. According to Gruenenthal, Germany, fewer than 10 patients were recruited for this study. No results were published
Sakamoto 1996	UK 420,000 units over 2 days versus sodium ozagrel 160 mg/d for 2 weeks in patients with acute lacunar infarction; follow-up 1 month. Testing ozagrel, not a direct thrombolytic (antiplatelet). Not relevant to this review
Seitz 2004	Excluded as it is testing tirofiban (antiplatelet) as adjunct to t-PA
Song 2000	Excluded as method of randomisation unclear. Only 21 days follow-up, no dependency data
Song 2003	Unclear method of randomisation, 14 days follow-up, no dependency data
TASS	Excluded because not randomised. This is an open-label dose-escalation study of TNK
Tazaki 1987	Not relevant to this review
TNK-TPA	Evaluating the effect of intravenous t-PA 0.9 mg/kg versus intravenous TNK 0.4 mg/kg in acute stroke patients with MCA occlusion. Excluded because it is a prospective case series, not a randomised study
Tsuchiya 1989	Confounded by heparin dose, e.g. higher-dose group plus heparin 2500 to 5000 U/day versus lower-dose group plus heparin 2500 U/day

Study	Reason for exclusion
Tsuchiya 1990	Confounded by heparin dose, e.g. higher-dose group plus heparin 2500 to 5000 U/day versus lower-dose group plus heparin 2500 U/day
TTT-AIS	Observational, not a randomised study. Evaluates 2 different doses of rt-PA
URICO-ICTUS	Intravenous uric acid (1 g) versus placebo control in acute ischaemic stroke patients treated with rt-PA and < 4.5 hours from onset. Effect of combined treatment on clinical outcome and infarction volume. Excluded as not testing thrombolysis, uric acid as adjunct to t-PA
VASTT	Phase IIA open-label dose-escalation study testing V10153. To the best of our knowledge this is not a randomised study. Study completed but no results published by the end of 2010
Wang 1999a	Intravenous defibrase 10 U for 7 days versus ahylsantinfarctase 2 U/d for 21 days in acute ischaemic stroke. Not a direct thrombolytic agent
Wang 2007h	Retrospective analysis of non-randomised case series
Won 2010	Abstract only. Observational - non-randomised
Wu 1995	Published as abstract in 1995. Trial of UK 300,000 IU/day for 3 days, then 100,000 IU/day for 7 days versus intravenous cerebrolysin (amount unspecified). No information on type of patients (N = 132), mode of randomisation or outcome measures or timing. Authors state that "curative rate, effective rate according to neurological deficit." Not possible to extract further data from the abstract. As far as we can see, never published in full. Therefore not usable
Xiao 2002	Intra-arterial carotid artery UK 300,000 U for 7 days versus intravenous UK 300,000 U for 7 days in acute ischaemic stroke patients. Only 21-day follow-up. No dependency data. Method of randomisation unclear
Xu 2000	Intravenous ahylsantinfarctase (20 U day 1, 10 U on 3rd and 5th day) plus from 6th day saliva miltiorrhiza (20 ml) versus intravenous defibrinogenase (10 U 1st day, 5 U on 3rd and 5th day) plus from 6th day saliva miltiorrhiza (20 ml) in ischaemic stroke. Neurological status and blood clotting monitored to 14 days. No functional outcome data. Excluded because of lack of relevant data and unclear whether randomised
Yan 1997	Streptokinase (1 million units over 1 hour) versus citicoline in acute ischaemic stroke. Citicoline is not a thrombolytic agent
Yoneda 1998	Open-label, dose escalating study of rt-PA (duteplase) 5, 10 or 20 MIU intra-arterially within 6 hours, acute major hemispheric syndrome, age under 80, angiographically proved MCA or ICA occlusion, exclude CT hypodensity, outcomes recanalisation at end of infusion, haemorrhage on CT, neurological status on hemispheric stroke scale at 1 month. No dependency data. Excluded because non-random, no long-term follow-up, no dependency data. 19 patients included in total
Zhang 2001e	Intra-arterial UK using Seldinger method (500,000 units) versus intravenous UK (750,000 units) in acute ischaemic stroke. Effect on recanalisation rate. The randomisation method is unclear. Only 21-day follow-up. No clinical outcomes available
Zhang 2006c	Edaravone + intravenous rt-PA versus rt-PA alone in acute ischaemic stroke. Not relevant to this review. Not testing thrombolysis
Zhou 1996b	Not relevant to this review. Not testing direct thrombolytic agent

CT: computed tomography

DSA: digital subtraction angiography

ESR: erythrocyte sedimentation rate

ICA: internal carotid artery
MCA: middle cerebral artery
rt-PA: recombinant t-PA
TNK: tenecteplase
t-PA: tissue plasminogen activator
UK: urokinase

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

Wadia 2009

Methods	Open-label, single-arm, multicentre, randomised trial
Participants	Acute ischaemic stroke within 4.5 hours of stroke onset
Interventions	Injection of tenecteplase (TNK-TPA)) 0.1 or 0.2 mg/kg bolus intravenously
Outcomes	Improvement at 24 hours. Symptomatic/asymptomatic haemorrhage at 36/48 hours. Outcomes at 7 days, 1 month, 3 months
Notes	

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

BASICS

Trial name or title	BASICS
Methods	Randomised, multicentre, open-label, controlled phase III, treatment trial
Participants	Patients with CTA or MRA confirmed basilar occlusion after completion of intravenous thrombolysis aged 18 to 85 years
Interventions	Patients will be randomised between additional intra-arterial therapy followed by maximum supportive care versus maximum supportive care alone. Intravenous thrombolysis has to be initiated within 4.5 hours from estimated time of basilar artery occlusion and intra-arterial therapy within 6 hours
Outcomes	Favourable outcome at day 90 defined as a mRS – functional scale of 0 to 3
Starting date	To be confirmed
Contact information	Wouter J Schonewille, St Antonius Hospital, University Medical Center Utrecht, The Netherlands
Notes	

DIAS-J

Trial name or title	Clinical study of desmoteplase in Japanese patients with acute ischaemic stroke (DIAS-J)
Methods	Randomised, double-blind, placebo-controlled, dose-escalation phase II trial
Participants	Diagnosis of acute ischaemic stroke, age 20 to 85 years, NIHSS 4 to 24, vessel occlusion of high-grade stenosis on angiography (MRA or CTA) in proximal cerebral arteries (TIMI 0 to 1)

Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke (Review)

DIAS-J (Continued)

Interventions	Single intravenous bolus of 70 or 90 µg/kg desmoteplase (dose-escalation design) within 3 to 9 hours after the onset of stroke symptoms
Outcomes	To evaluate the safety and tolerability of desmoteplase doses of 70 µg/kg and 90 µg/kg in Japanese patients with acute ischaemic stroke as measured by the presence of SICH within 72 hours after investigational medicinal product; evaluate the clinical improvement at day 90 after administration of investigational medicinal product as measured by the mRS; evaluate the clinical improvement at days 7 and 30 after administration of investigational medicinal product as measured by the mRS; evaluate recanalisation at 18 ± 6 hours after administration of investigational medicinal product; evaluate change in infarct size at 18 ± 6 hours relative to pre-treatment infarct size; evaluate the pharmacokinetics and pharmacodynamics of desmoteplase at 0.5 to 9 hours; evaluate the immunogenicity of desmoteplase at day 7, day 30, day 90; explore the predictive value of different volumes of absolute mismatch for the clinical response and other objectives at day 90
Starting date	1 August 2010
Contact information	Rudiger von Kummer, Dresden, Germany, kummer-r@rcs.urz.tu-dresden.de OR H. Lundbeck A/S, LundbeckClinicalTrials@lundbeck.com
Notes	

ENCHANTED

Trial name or title	Enhanced control of hypertension and thrombolysis stroke study (ENCHANTED)
Methods	Randomised controlled trial, 2 arms
Participants	Age ≥ 18 years, fulfil local criteria for use of intravenous rt-PA, < 3 or < 4.5 hours of definite time of stroke onset, systolic BP ≤ 185 mmHg, provide written informed consent or approved surrogate and no definite indication/contraindication for either dose of rt-PA (Arm A) or systolic BP ≥ 150 mm HG and no definite indication/contraindication to intensive BP lowering to 140 to 150 mmHg range over next 72 hours (Arm B)
Interventions	Arm A: low-dose rt-PA (0.6 mg/kg intravenous alteplase, 15% bolus, 85% infusion over 60 minutes); standard-dose rt-PA (0.9 mg/kg intravenous alteplase, 10% bolus, 90% infusion over 60 minutes) Arm B: intensive BP lowering (aim for target BP of 140 to 150 mmHg, to be achieved within 30 minutes, to be sustained for at least 72 hours, use locally available agents, patient to be monitored in an appropriate facility such as neurointensive care unit, acute stroke unit, high dependency unit)
Outcomes	mRS of 0 to 1 at 90 days; combined death and any disability mRS of 2 to 6 at 90 days
Starting date	October 2011
Contact information	Craig Anderson, canderson@georgeinstitute.org.au; Richard Lindley, richard.lindley@sydney.edu.au
Notes	

FRALYSE

Trial name or title	FRALYSE
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FRALYSE (Continued)

Methods	Single-blinded randomised trial
Participants	All types of cerebral infarction < 7 hours from stroke onset. Exclude patients with hypodense infarct on CT
Interventions	0.9 mg/kg intravenously over 60 minutes versus 0.8 mg/kg intravenously over 90 minutes
Outcomes	3-month neurological score; haemorrhage on 24-hour CT
Starting date	2001 to 2008: 373 patients had been included.
Contact information	P Trouillas, Cerebrovascular Disease Centre, Lyon, France.
Notes	Heparin not allowed until 24 hours after treatment. An MR substudy arm with 65 patients. 5 French centres involved. 80% of patients treated > 3 hours after onset

ITAIS

Trial name or title	Imaging-based Thrombolysis trial in Acute Ischemic Stroke (ITAIS)
Methods	
Participants	Multicentre trial, China 3 to 6 hours post stroke onset with perfusion/diffusion mismatch on MRI
Interventions	Intravenous versus intra-arterial rt-PA
Outcomes	mRS at 90 days, intracerebral haemorrhage
Starting date	2005
Contact information	
Notes	

BP: blood pressure
 CT: computed tomography
 CTA: CT angiography
 MR: magnetic resonance
 MRA: magnetic resonance angioplasty
 MRI: magnetic resonance imaging
 mRS: modified Rankin Score
 NIHSS: National Institutes of Neurological Disorders and Stroke Scale
 rt-PA: recombinant tissue plasminogen activator
 SICH: symptomatic intracranial haemorrhage
 TIMI scale: Thrombolysis In Myocardial Infarction scale

DATA AND ANALYSES

Comparison 1. Thrombolysis: higher dose versus lower dose of the same agent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependency at end of follow-up	7	630	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.62, 1.19]
1.1 t-PA	1	19	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.20, 7.01]
1.2 Urokinase	1	317	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.52, 1.32]
1.3 Desmoteplase	3	182	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.49, 1.57]
1.4 Tenecteplase	2	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.37, 1.90]
2 Death from all causes within about the first two weeks	10	1291	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.66, 1.80]
2.1 t-PA	5	496	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.45, 2.20]
2.2 Urokinase	3	643	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.49, 2.06]
2.3 Desmoteplase	2	152	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.12 [0.47, 9.62]
3 Total deaths from all causes at end of follow-up	12	1403	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.82, 1.80]
3.1 t-PA	5	496	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.37, 1.52]
3.2 Urokinase	3	643	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.57, 2.00]
3.3 Desmoteplase	2	152	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.21 [1.23, 8.39]
3.4 Tenecteplase	2	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [0.53, 5.32]
4 'Significant' intracranial haemorrhage during follow-up	13	1433	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [0.81, 2.52]
4.1 t-PA	5	496	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.57, 2.76]
4.2 Urokinase	3	643	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.86 [0.64, 5.38]
4.3 Desmoteplase	3	182	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.17, 4.48]
4.4 Tenecteplase	2	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.77 [0.38, 20.03]
5 Fatal intracranial haemorrhage during follow-up	10	1274	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.71 [1.22, 6.04]
5.1 t-PA	4	429	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.64 [1.28, 16.87]
5.2 Urokinase	3	643	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.32 [0.66, 8.10]
5.3 Desmoteplase	2	152	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.41 [0.33, 17.63]
5.4 Tenecteplase	1	50	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]

Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke (Review)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Total major (including fatal) extracranial haemorrhage during follow-up	9	1154	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.72 [0.93, 3.21]
6.1 t-PA	3	297	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Urokinase	3	643	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [0.88, 3.91]
6.3 Desmoteplase	2	152	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.39, 4.09]
6.4 Tenecteplase	1	62	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]

Analysis 1.1. Comparison 1 Thrombolysis: higher dose versus lower dose of the same agent, Outcome 1 Death or dependency at end of follow-up.

Analysis 1.2. Comparison 1 Thrombolysis: higher dose versus lower dose of the same agent, Outcome 2 Death from all causes within about the first two weeks.

Analysis 1.3. Comparison 1 Thrombolysis: higher dose versus lower dose of the same agent, Outcome 3 Total deaths from all causes at end of follow-up.

Analysis 1.4. Comparison 1 Thrombolysis: higher dose versus lower dose of the same agent, Outcome 4 'Significant' intracranial haemorrhage during follow-up.

Analysis 1.5. Comparison 1 Thrombolysis: higher dose versus lower dose of the same agent, Outcome 5 Fatal intracranial haemorrhage during follow-up.

Analysis 1.6. Comparison 1 Thrombolysis: higher dose versus lower dose of the same agent, Outcome 6 Total major (including fatal) extracranial haemorrhage during follow-up.

Comparison 2. Thrombolysis: one agent versus another

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependency at the end of follow-up	2	187	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.58 [0.31, 1.09]
1.1 Tenecteplase vs t-PA	2	187	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.58 [0.31, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Death from all causes within about the first two weeks	3	688	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.38, 2.77]
2.1 Tissue-cultured urokinase (newer drug) vs urokinase (control)	1	170	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [0.23, 8.09]
2.2 t-PA (newer drug) vs urokinase (control)	2	518	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.27, 2.98]
3 Total deaths from all causes at end of follow-up	5	875	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.38, 1.31]
3.1 Tissue-cultured urokinase (newer drug) vs urokinase (control)	1	170	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.81 [0.36, 9.19]
3.2 t-PA (newer drug) vs urokinase (control)	2	518	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.72 [0.26, 2.02]
3.3 Tenecteplase (newer drug) vs rt-PA (control)	2	187	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.21, 1.27]
4 'Significant' intracranial haemorrhage during follow-up	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Tissue-cultured urokinase (newer drug) vs urokinase (control)	1	170	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.00, 6.21]
4.2 t-PA (newer drug) vs urokinase (control)	2	518	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.26 [0.06, 1.18]
4.3 Tenecteplase (newer drug) vs rt-PA (control)	2	187	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.20, 2.76]
5 Fatal intracranial haemorrhage during follow-up	4	763	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.12, 13.86]
5.1 Tissue-cultured urokinase (newer drug) vs urokinase (control)	1	170	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 t-PA (newer drug) vs urokinase (control)	2	518	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.91 [0.16, 399.51]
5.3 Tenecteplase (newer drug) vs rt-PA (control)	1	75	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.47 [0.02, 9.02]
6 Total major (including fatal) extracranial haemorrhage during follow-up	4	800	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [0.15, 16.27]
6.1 Tissue-cultured urokinase (newer drug) vs urokinase (control)	1	170	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 t-PA (newer drug) vs urokinase (control)	2	518	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.07, 17.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Tenecteplase (newer drug) vs rt-PA (control)	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.99 [0.05, 318.43]

Analysis 2.1. Comparison 2 Thrombolysis: one agent versus another, Outcome 1 Death or dependency at the end of follow-up.

Analysis 2.2. Comparison 2 Thrombolysis: one agent versus another, Outcome 2 Death from all causes within about the first two weeks.

Study or subgroup	Newer drug n/N	UK or rt-PA n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Test for overall effect: $Z=0.05$ ($P=0.96$)					
Test for subgroup differences: $\text{Chi}^2=0.14$, $\text{df}=1$ ($P=0.7$), $I^2=0\%$					
<div> <div>Newer drug better</div> <div>0.020.111050</div> <div>UK or rt-PA drug better</div> </div>					

Analysis 2.3. Comparison 2 Thrombolysis: one agent versus another, Outcome 3 Total deaths from all causes at end of follow-up.

Study or subgroup	Newer drug n/N	UK or rt-PA n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.3.1 Tissue-cultured urokinase (newer drug) vs urokinase (control)					
Ohtomo 1985	4/89	2/81		14.76%	1.81[0.36,9.19]
Subtotal (95% CI)	89	81		14.76%	1.81[0.36,9.19]
Total events: 4 (Newer drug), 2 (UK or rt-PA)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.71$ ($P=0.48$)					
2.3.2 t-PA (newer drug) vs urokinase (control)					
Ohtomo 1988b	6/176	6/188		29.53%	1.07[0.34,3.38]
Abe 1990	0/71	3/83		7.48%	0.15[0.02,1.5]
Subtotal (95% CI)	247	271		37%	0.72[0.26,2.02]
Total events: 6 (Newer drug), 9 (UK or rt-PA)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=2.23$, $\text{df}=1$ ($P=0.14$); $I^2=55.11\%$					
Test for overall effect: $Z=0.62$ ($P=0.53$)					
2.3.3 Tenecteplase (newer drug) vs rt-PA (control)					
TNK-S2B	12/81	8/31		33.72%	0.48[0.16,1.4]
Parsons 2012	4/50	3/25		14.52%	0.63[0.12,3.23]
Subtotal (95% CI)	131	56		48.24%	0.52[0.21,1.27]
Total events: 16 (Newer drug), 11 (UK or rt-PA)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=0.08$, $\text{df}=1$ ($P=0.78$); $I^2=0\%$					
Test for overall effect: $Z=1.44$ ($P=0.15$)					
Total (95% CI)	467	408		100%	0.7[0.38,1.31]
Total events: 26 (Newer drug), 22 (UK or rt-PA)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=4.05$, $\text{df}=4$ ($P=0.4$); $I^2=1.18\%$					
Test for overall effect: $Z=1.1$ ($P=0.27$)					
Test for subgroup differences: $\text{Chi}^2=1.74$, $\text{df}=1$ ($P=0.42$), $I^2=0\%$					
<div> <div>Newer drug better</div> <div>0.020.111050</div> <div>UK or rt-PA better</div> </div>					

Analysis 2.4. Comparison 2 Thrombolysis: one agent versus another, Outcome 4 'Significant' intracranial haemorrhage during follow-up.

Study or subgroup	Newer drug n/N	UK or rt-PA n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.4.1 Tissue-cultured urokinase (newer drug) vs urokinase (control)					
Ohtomo 1985	0/89	1/81		100%	0.12[0,6.21]
Subtotal (95% CI)	89	81		100%	0.12[0,6.21]
<div> <div>Newer drug better</div> <div>0.0010.11101000</div> <div>UK or rt-PA better</div> </div>

Analysis 2.5. Comparison 2 Thrombolysis: one agent versus another, Outcome 5 Fatal intracranial haemorrhage during follow-up.

Analysis 2.6. Comparison 2 Thrombolysis: one agent versus another, Outcome 6 Total major (including fatal) extracranial haemorrhage during follow-up.

Comparison 3. Thrombolysis: different routes of administration of the same agent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependency at end of follow-up	4	478	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.75, 1.55]
1.1 rt-PA	3	451	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.72, 1.51]
1.2 Urokinase	1	27	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.07 [0.45, 9.58]
2 Death from all causes within about the first two weeks	5	485	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.51, 1.79]
2.1 rt-PA	4	458	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.46, 1.79]
2.2 Urokinase	1	27	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.24, 7.14]
3 Total deaths from all causes at end of follow-up	4	458	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.47, 1.39]
3.1 rt-PA	4	458	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.47, 1.39]
3.2 Urokinase	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 'Significant' intracranial haemorrhage during follow-up	5	485	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.54, 2.25]
4.1 rt-PA	4	458	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.61, 2.68]
4.2 Urokinase	1	27	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.01, 1.95]
5 Fatal intracranial haemorrhage during follow-up	5	485	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.21, 2.11]
5.1 rt-PA	4	458	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.27, 3.33]
5.2 Urokinase	1	27	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.01, 1.95]

Analysis 3.1. Comparison 3 Thrombolysis: different routes of administration of the same agent, Outcome 1 Death or dependency at end of follow-up.

Analysis 3.2. Comparison 3 Thrombolysis: different routes of administration of the same agent, Outcome 2 Death from all causes within about the first two weeks.

Analysis 3.3. Comparison 3 Thrombolysis: different routes of administration of the same agent, Outcome 3 Total deaths from all causes at end of follow-up.

Analysis 3.4. Comparison 3 Thrombolysis: different routes of administration of the same agent, Outcome 4 'Significant' intracranial haemorrhage during follow-up.

Analysis 3.5. Comparison 3 Thrombolysis: different routes of administration of the same agent, Outcome 5 Fatal intracranial haemorrhage during follow-up.

APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE (Ovid) 1966 to May 2012

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. thrombolytic therapy/
6. fibrinolytic agents/ or plasmin/ or plasminogen/ or tissue plasminogen activator/ or exp plasminogen activators/ or urokinase-type plasminogen activator/
7. fibrinolysis/
8. (thromboly\$ or fibrinoly\$ or recanaliz\$ or recanaliz\$).tw.
9. ((clot\$ or thrombus) adj5 (lyse or lysis or dissolve\$ or dissolution)).tw.
10. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
11. (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 retevase).tw.
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Randomized Controlled Trials as Topic/
14. random allocation/
15. Controlled Clinical Trials as Topic/
16. control groups/
17. 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/
18. double-blind method/
19. single-blind method/
20. Placebos/
21. placebo effect/
22. Drug Evaluation/
23. Research Design/
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
27. (random\$ or RCT or RCTs or quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw
28. (controlled adj5 (trial\$ or stud\$)).tw.
29. (clinical\$ adj5 trial\$).tw.
30. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
31. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
32. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
33. placebo\$.tw.
34. (assign\$ or allocat\$).tw.
35. controls.tw.
36. trial.ti.
37. or/13-36
38. 4 and 12 and 37
39. exp animals/ not humans.sh.
40. 38 not 39

Appendix 2. EMBASE search strategy

EMBASE (Ovid) 1980 to May 2012

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 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. fibrinolytic therapy/
6. fibrinolytic agent/ or plasmin/ or plasminogen/ or exp plasminogen activator/
7. blood clot lysis/
8. fibrinolysis/
9. (thromboly\$ or fibrinoly\$ or recanaliz\$ or recanaliz\$).tw.
10. ((clot\$ or thrombus) adj5 (lyse or lysis or dissolve\$ or dissolution)).tw.
11. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
12. (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 retevase).tw.
13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. Randomized Controlled Trial/
15. Randomization/

16. Controlled Study/
17. control group/
18. 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/
19. Double Blind Procedure/
20. Single Blind Procedure/ or triple blind procedure/
21. placebo/
22. drug comparison/ or drug dose comparison/
23. "types of study"/
24. (random\$ or RCT or RCTs or quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw
25. (controlled adj5 (trial\$ or stud\$)).tw.
26. (clinical\$ adj5 trial\$).tw.
27. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
28. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
29. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
30. placebo\$.tw.
31. (assign\$ or allocat\$).tw.
32. trial.ti.
33. or/14-32
34. 4 and 13 and 33
35. (ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/) and HUMAN/
36. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
37. 36 not 35
38. 34 not 37

FEEDBACK

Comment

Summary

The reviewers found a five-fold increase in intracerebral haemorrhage comparing high with low dose thrombolysis. This is discussed in the review and while the finding is not methodologically robust enough to make definitive statements, this potential adverse effect is so important that it should be mentioned in the conclusions of the review. There also should be more discussion of the Wardlaw et al Cochrane review (and Lancet 1997) which indicated a significant (nearly five-fold) increase in intracranial haemorrhage with thrombolysis.

Reply

It is important to note that there are very few data in the review at present comparing doses of thrombolytic drugs. Hence, it is difficult to draw any firm conclusions. While the notion that a higher dose of a drug might cause more symptomatic intracranial haemorrhage seems logical, and fits with other data, the fact is that the data in the review are scant. We believe that over-emphasis of these data would be potentially misleading. There are no data on the relative benefits of a higher dose of drug versus a lower dose and it is entirely possible that a higher dose has greater long-term benefit in terms of functional outcome, albeit at an increased risk of early hazard from symptomatic haemorrhage. However, further trials would be required to provide more robust data to sort out these relationships. Hence, we will leave the conclusions section unamended.

Contributors

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WHAT'S NEW

Date	Event	Description
19 March 2013	New citation required but conclusions have not changed	There has been no change to the conclusions of the review
19 March 2013	New search has been performed	The review has been updated with the inclusion of 10 trials. It now has 20 included trials involving 2165 participants. The text has been revised throughout

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 4, 1998

Date	Event	Description
14 October 2008	Amended	Converted to new review format.
22 October 2003	New search has been performed	For this first update of the review, two trials have been added.

CONTRIBUTIONS OF AUTHORS

JMW and ML contributed to literature searching, collection of data, extraction of data, and interpretation of data of the first version of the review. ML and JMW drafted the review and produced the first version for publication.

Orell Mielke and JMW carried out searches for the first revised review, extracted the data, performed the analyses and, with ML, drafted and updated the review.

PK and JMW carried out searches for the second revised review, extracted the data, performed the analyses, drafted and updated the review and, with ML, checked the final version for submission.

DECLARATIONS OF INTEREST

JMW (and other academic colleagues) was awarded grants to perform the Third International Stroke Trial, a multicentre international randomised controlled trial of rt-PA versus control in acute ischaemic stroke. The funders included the UK Medical Research Council, the Emerging Medicines Evaluation initiative of the National Institutes of Health Research UK, the Stroke Association, and numerous other governmental and charitable funders. These grants were all administered by the University of Edinburgh and funded staff, equipment and consumables. I received no personal salary or other direct funding from any of these.

Many years ago, the University of Edinburgh established a Brain Research Imaging Centre Magnetic Resonance scanner with academic government grants and some collaborative support from industry. The Industry funders were the MR equipment manufacturer Elscint (now taken over by GE) who provided the majority industry investment, Boehringer Ingelheim and Novartis, both of whom provided small contributions worth less than 5% of the total cost of the facility.

PK and ML have no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- University of Edinburgh, Scotland, UK.
- University of Edinburgh, UK.

This work was undertaken as part of the MSc in Neuroimaging for Research (a final year project) University of Edinburgh, 2010-2011

External sources

- Medical Research Council, UK.
- University of Heidelberg - Faculty of Medicine Mannheim, Germany.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Not applicable.

INDEX TERMS

Medical Subject Headings (MeSH)

*Thrombolytic Therapy [adverse effects]; Acute Disease; Brain Ischemia [*drug therapy]; Cerebral Hemorrhage [*chemically induced] [epidemiology]; Fibrinolytic Agents [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic;

Stroke [*drug therapy]; Tenecteplase; Tissue Plasminogen Activator [administration & dosage] [adverse effects]; Urokinase-Type Plasminogen Activator [administration & dosage] [adverse effects]

MeSH check words

Humans