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[Intervention Review]

Thrombolysis for acute ischaemic stroke

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ABSTRACT

Background

Most strokes are due to blockage of an artery in the brain by a blood clot. Prompt treatment with thrombolytic drugs can restore blood flow before major brain damage has occurred and improve recovery after stroke in some people. Thrombolytic drugs, however, can also cause serious bleeding in the brain, which can be fatal. One drug, recombinant tissue plasminogen activator (rt-PA), is licensed for use in selected patients within 4.5 hours of stroke in Europe and within three hours in the USA. There is an upper age limit of 80 years in some countries, and a limitation to mainly non-severe stroke in others. Forty per cent more data are available since this review was last updated in 2009.

Objectives

To determine whether, and in what circumstances, thrombolytic therapy might be an effective and safe treatment for acute ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched November 2013), MEDLINE (1966 to November 2013) and EMBASE (1980 to November 2013). We also handsearched conference proceedings and journals, searched reference lists and contacted pharmaceutical companies and trialists.

Selection criteria

Randomised trials of any thrombolytic agent compared with control in people with definite ischaemic stroke.

Data collection and analysis

Two review authors applied the inclusion criteria, extracted data and assessed trial quality. We verified the extracted data with investigators of all major trials, obtaining additional unpublished data if available.

Main results

We included 27 trials, involving 10,187 participants, testing urokinase, streptokinase, rt-PA, recombinant pro-urokinase or desmoteplase. Four trials used intra-arterial administration, while the rest used the intravenous route. Most data come from trials that started treatment up to six hours after stroke. About 44% of the trials (about 70% of the participants) were testing intravenous rt-PA. In earlier studies very few of the participants (0.5%) were aged over 80 years; in this update, 16% of participants are over 80 years of age due to the inclusion of IST-3 (53% of participants in this trial were aged over 80 years). Trials published more recently utilised computerised randomisation, so there are less likely to be baseline imbalances than in previous versions of the review. More than 50% of trials fulfilled criteria for high-grade concealment; there were few losses to follow-up for the main outcomes.

Thrombolytic therapy, mostly administered up to six hours after ischaemic stroke, significantly reduced the proportion of participants who were dead or dependent (modified Rankin 3 to 6) at three to six months after stroke (odds ratio (OR) 0.85, 95% confidence interval (CI) 0.78 to 0.93). Thrombolytic therapy increased the risk of symptomatic intracranial haemorrhage (OR 3.75, 95% CI 3.11 to 4.51), early death (OR 1.69, 95% CI 1.44 to 1.98; 13 trials, 7458 participants) and death by three to six months after stroke (OR 1.18, 95% CI 1.06 to 1.30). Early death after thrombolysis was mostly attributable to intracranial haemorrhage. Treatment within three hours of stroke was more effective in reducing death or dependency (OR 0.66, 95% CI 0.56 to 0.79) without any increase in death (OR 0.99, 95% CI 0.82 to 1.21; 11 trials, 2187 participants). There was heterogeneity between the trials. Contemporaneous antithrombotic drugs increased the risk of death. Trials testing rt-PA showed a significant reduction in death or dependency with treatment up to six hours (OR 0.84, 95% CI 0.77 to 0.93, P = 0.0006; 8 trials, 6729 participants) with significant heterogeneity; treatment within three hours was more beneficial (OR 0.65, 95% CI 0.54 to 0.80, P < 0.0001; 6 trials, 1779 participants) without heterogeneity. Participants aged over 80 years benefited equally to those aged under 80 years, particularly if treated within three hours of stroke.

Authors' conclusions

Thrombolytic therapy given up to six hours after stroke reduces the proportion of dead or dependent people. Those treated within the first three hours derive substantially more benefit than with later treatment. This overall benefit was apparent despite an increase in symptomatic intracranial haemorrhage, deaths at seven to 10 days, and deaths at final follow-up (except for trials testing rt-PA, which had no effect on death at final follow-up). Further trials are needed to identify the latest time window, whether people with mild stroke benefit from thrombolysis, to find ways of reducing symptomatic intracranial haemorrhage and deaths, and to identify the environment in which thrombolysis may best be given in routine practice.

PLAIN LANGUAGE SUMMARY

Clot-dissolving drugs for treating ischaemic stroke in the early stages

Question

We wanted to compare the safety and efficacy of clot-dissolving (thrombolytic) drugs versus placebo or no treatment in the early stages of ischaemic stroke to see if clot-dissolving drugs improve outcome after stroke.

Background

Most strokes are due to blockage of an artery in the brain by a blood clot. Prompt treatment with clot-dissolving (thrombolytic) drugs can restore blood flow before major brain damage has occurred and could mean that people are more likely to make a good recovery from their stroke. Thrombolytic drugs can also, however, cause serious bleeding in the brain, which can be fatal. Thrombolytic therapy has now been evaluated in many randomised trials in acute ischaemic stroke. The thrombolytic drug alteplase has been licensed for use within three hours of stroke in the USA and Canada, and within 4.5 hours in most European countries. The numbers of people receiving this treatment successively are increasing.

Study characteristics

We identified 27 trials with a total of 10,187 participants in searches conducted up to November 2013. Most data come from trials testing one drug (recombinant tissue Plasminogen Activator, rt-PA) given into a vein up to six hours after acute ischaemic stroke, but several other drugs were also tested and at different times to treatment after stroke and given into an artery in the brain rather than into a vein in the arm. All trials compared a clot-dissolving drug with a placebo (control) group. Most trials included participants with moderate to severe stroke. All trials took place in hospitals that were used to treating people with stroke. Differences between trials mean that not all trials contribute information to all outcomes, but we have used all available data. Most trials included participants after a computed tomography (CT) brain scan had excluded a brain haemorrhage as the cause of symptoms (a few trials used magnetic resonance brain scanning instead).

Key results

There is general agreement between the earlier trials and the one recent trial added in this update (IST-3) for all main outcomes, and between the 12 trials that tested rt-PA and the 15 trials that tested other clot-dissolving drugs. The main difference between IST-3 and earlier trials was that IST-3 had many participants above 80 years. Clot-dissolving treatment can reduce the risk of long-term dependency on others for daily activities, in spite of there being an increased risk of bleeding in the brain which also increased the risk of early death. Once the early bleeding risk had passed, at three or six months after stroke, people given clot-dissolving drugs were more likely to have recovered from their stroke and to be independent, especially if they had been treated within the first three hours after stroke. Older people benefited as much as younger people. Giving aspirin at the same time as clot-busting drugs increased the risk of bleeding and should be avoided. Further analyses of individual patient data factors such as findings on brain scanning before treatment, and of different ways of giving the treatment, may give more information than the summary data that we used here. Meantime, people who think that they are experiencing a stroke should get to hospital quickly, be assessed by a stroke doctor, have a brain scan and receive clot-dissolving treatment as fast as possible. They should not hesitate by thinking that they will be 'too old' for treatment. The treatment is very effective if started within three hours of stroke and definitely improves outcome if given up to 4.5 hours after stroke, but later than that the effects are less clear

and are still being tested in trials. More information is needed from trials in people with mild stroke to see if the benefit of clot-dissolving drugs outweighs the risk of haemorrhage.

Quality of the evidence

The evidence comes mostly from well-conducted randomised trials run by stroke experts. Some trials (8/27) were run by companies that make the clot-dissolving drugs, but most trials (19/27, including most participants) were funded by Government or charity sources independently of drug companies. These results apply to a wide range of people with a wide range of severities of stroke and other medical conditions.

BACKGROUND

Description of the condition

Acute ischaemic stroke is a major cause of death and disability worldwide. Most strokes are due to blockage of an artery in the brain by a blood clot (ischaemic stroke) e.g. from the heart or neck arteries.

Description of the intervention

Thrombolytic drugs derive from naturally-occurring enzymes that dissolve thrombus as part of the natural clotting cascade. Some are extracted from biological samples (e.g. urokinase, desmoteplase) and others are manufactured (e.g. recombinant tissue plasminogen activator (rt-PA), or recombinant pro-urokinase).

How the intervention might work

Clot-dissolving (thrombolytic) drugs may reduce brain damage from a stroke by restoring the blood flow if given rapidly enough after stroke, but may also cause serious bleeding in the brain.

Why it is important to do this review

An overview of the literature on thrombolysis in acute ischaemic stroke in 1992 (Wardlaw 1992) identified six randomised trials of various thrombolytic drugs including a total of just 700 participants. A Cochrane review published in 1995 (Wardlaw 1995) updated the original 1992 review. It was updated again in 1999 (3478 participants in total) (Wardlaw 1999), in 2003 (5727 participants) (Wardlaw 2003b), in 2009 (7152 participants) (Wardlaw 2009) but even so, many essential questions remained unanswered: How big is the overall benefit? What is the latest time window in which the treatment is still beneficial? Which grades of stroke severity and which types of stroke, as judged clinically and on brain imaging, are more likely to respond favourably to treatment? Should people aged over 80 years receive thrombolysis? Which types of patients are most likely to be harmed by treatment, and which to benefit from it (e.g. with or without other major medical conditions like cardiac arrhythmias, diabetes, hypertension, or other disorders and concomitant medication) (Wardlaw 2002)? To answer these questions reliably, and in particular to be able to tailor treatment to the individual, more data are needed from new randomised controlled trials (RCTs).

Meanwhile, the thrombolytic drug alteplase (rt-PA) was licensed for use within three hours of stroke in the USA and Canada, and up to 4.5 hours in most European countries, and an increasing number of people now receive the treatment. Guidelines recommended that thrombolysis should be delivered by a clinical team with suitable training and experience and in a setting with appropriate facilities (ESO Stroke Guidelines 2008; NICE Stroke Guideline 2008). A general review of the use of thrombolytic therapy in clinical practice and the clinical service required to deliver it was provided in a book on the management of stroke (Warlow 2008).

This updated review includes all trials completed and made public since 2009, as well as additional data published since 2009 from trials included in earlier versions of the review. The total number of participants is now 10,187, more than a 10-fold increase since the review was initiated in 1990 and an increase of more than 40% since 2009. Although many of the data now come from trials testing intravenous rt-PA within the first six hours after stroke onset, the more recent trials are exploring alternative methods for selecting participants and extending time windows, e.g. through use of advanced brain imaging. The upper age limit of 80 years, stroke severity and new imaging data are also analysed. This systematic review includes these data and provides a convenient and up-to-date summary of the evidence.

OBJECTIVES

To determine whether, and in what circumstances, thrombolytic therapy might be an effective and safe treatment for acute ischaemic stroke. We wished to determine whether:

1. thrombolytic therapy increases the risk of death:
   a. within the first two weeks of stroke; or
   b. at long-term follow-up;
2. thrombolytic therapy increases the risk of symptomatic or fatal intracranial haemorrhage, or symptomatic infarct swelling;
3. thrombolysis reduces the proportion of people dead or dependent at long-term follow-up, in spite of any early hazard, so that there is an overall net benefit.

We wished to undertake exploratory analyses to examine whether:

1. thrombolytic therapy interacts with antithrombotic therapy to increase the hazard;
2. the balance of risk and benefit with thrombolytic therapy may vary with the severity of the stroke;
3. the latest therapeutic time window for effective treatment can yet be determined;
4. whether the effect of thrombolysis is different in people aged over 80 compared with under 80 years of age;
5. whether people selected for treatment using MR diffusion/perfusion imaging had better effect of thrombolytic treatment than those selected using computed tomography (CT) brain imaging;
6. whether individual findings on CT brain imaging identified people in whom the effect of thrombolysis was different;
7. whether the effect of intra-arterial therapy differed from intravenous therapy and explained any of the heterogeneity.

METHODS

Criteria for considering studies for this review

Types of studies

We sought to identify all truly randomised unconfounded trials of thrombolytic therapy compared with placebo or open control in people with acute ischaemic stroke. We excluded trials that were not truly randomised, such as dose-range-finding studies, and trials that included thrombolytic treatment in the control group. We included trials in which the exact method of randomisation was unknown, even after correspondence with the authors, if the available information suggested that the randomisation was not likely to be biased. We also included trials that were not originally analysed on an intention-to-treat basis if information on outcome could be obtained for all randomised participants, thus allowing us to perform an intention-to-treat analysis.

Types of participants

We included trials of participants with a definite acute ischaemic stroke (CT or magnetic resonance (MR) scanning having excluded intracranial haemorrhage prior to randomisation).

Types of interventions

We included all types of thrombolytic drug, given in any dose, by the intravenous or intra-arterial route: urokinase (UK, also known as u-PA), recombinant pro-urokinase (rpro-UK), streptokinase (SK), recombinant tissue plasminogen activator (rt-PA) including duteplase, lumbrokinase (LK), and desmoteplase.

We excluded trials that were confounded by the treatment or control group receiving another active therapy which had not been factored in to the randomisation (for example, thrombolytic drug plus another agent versus placebo, or thrombolytic drug versus another agent).

Types of outcome measures

The primary outcome measures were death or dependency, as defined by modified Rankin score of 3 to 6, and death at the end of follow-up. We considered all other outcomes as secondary.

We assessed the following.

1. Deaths from all causes within the first seven to 10 days after treatment.
2. Symptomatic intracranial haemorrhage (SICH): either symptomatic (that is, temporally associated with a deterioration in the person's neurological state), or fatal (that is, leading directly to death), and occurring within the first seven to 10 days. Note that symptomatic intracranial haemorrhage includes haemorrhagic transformation of the infarct, haemorrhage elsewhere in the brain remote from the infarct, and haemorrhage into the spaces surrounding the brain. Definitions of SICH vary between trials and therefore we have used the SICH data as defined by each trial's primary definition rather than attempting to standardise the definition.
3. Fatal intracranial haemorrhage.
4. Deaths within the first seven to 10 days not due to intracranial haemorrhage.
5. Symptomatic infarct swelling (oedema).
6. Deaths occurring between the end of the first seven to 10 days and three to six months.
7. Deaths from all causes during the whole trial follow-up period.
8. Poor functional outcome at the end of follow-up. This was the primary outcome measure for the review and was defined as death or dependency, measured by the modified Rankin or Barthel scales, at the end of the trial follow-up period. Poor functional outcome (the converse of good functional outcome) is the most clinically relevant and important measure of outcome, since the aim of treatment should be not merely to avoid death but also to decrease dependency among the survivors; that is, to increase the proportion of independent survivors and conversely to reduce the risk of survival with serious disability. Dependency in the present analysis was defined as a score of between 3 and 5 inclusive on the modified Rankin Scale (mRS). Some would prefer a definition of 'good outcome' (independence) including Rankin 0 and 1 only; therefore, wherever possible we sought data on the number of participants in each individual Rankin category so as to compare poor functional outcome defined as mRS 2 to 6 with the definition of 3 to 6. Where data were not available for mRS 3 to 6, we used mRS 2 to 6 instead, rather than excluding the trial from analysis.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We searched for all trials in all languages using the following overlapping methods, and arranged translation of relevant papers published in languages other than English.

Electronic searches

We searched the Cochrane Stroke Group's Trials Register, which was last searched by the Managing Editor on 18 November 2013. In addition, we carried out comprehensive searches of MEDLINE (Ovid) (1966 to November 2013) (Appendix 1) and EMBASE (Ovid) (1980 to November 2013) (Appendix 2). We developed the search strategies for MEDLINE and EMBASE with the help of the Cochrane Stroke Group Trials Search Co-ordinator.

Searching other resources

1. We handsearched the following conference proceedings and stroke and neurological journals: *Stroke*, *Cerebrovascular Diseases*, *International Journal of Stroke*, *Journal of Stroke and Cerebrovascular Diseases*, *Neurology* and *Journal of Neurology, Neurosurgery and Psychiatry* published to March 2014.
2. We checked multiple international conference proceedings on stroke and specifically on thrombolysis since 1991. These include all European Stroke Conferences (since 1992, annual since 1994), all International Stroke Conferences hosted by the American Heart Association (annual), all World Stroke Conferences (biannual), all Thrombolysis in Acute Ischaemic Stroke symposia (biannual).
3. We examined reference lists quoted in thrombolytic therapy papers.
4. We made direct contact with principal investigators of trials in Europe, North America, Japan, China, and Australasia.
5. We have been in regular contact with the manufacturer of rt-PA, and other companies involved in ongoing studies of thrombolysis identified from the Washington Internet Stroke Center Register of ongoing trials (www.strokecenter.org).

For previous versions of this review:

1. We handsearched the following journals from 1979 to April 1994: *Japanese Journal of Stroke, Clinical Evaluation, Japanese Journal of Pharmacology & Therapeutics,* and *Rinsho Ketsueki (*we obtained translations of the non-English language publications from people in whose native language the paper was published);
2. We contacted 321 pharmaceutical companies for more information about trials known to exist from the above efforts, and for information on any trials which were so far unknown to us (the last systematic contact was made in December 1997); all companies except one (which was known to be doing a trial in any case) responded, and no trials were identified that we did not already know about.

Data collection and analysis

This review builds on a continuous data collection process that started in 1989.

Selection of studies

Two review authors (JW, VM) screened the records obtained from the electronic searches and excluded obviously irrelevant studies. We obtained the full paper copy of the remaining studies and the same two review authors selected truly randomised trials comparing a thrombolytic drug with placebo or open control in people with acute ischaemic stroke, brain imaging having excluded cerebral haemorrhage and other structural causes of stroke-like symptoms. We sought additional unpublished information from the principal investigators of all the trials that appeared to meet our inclusion criteria. We resolved any disagreements by discussion. The selection for 2003 update was verified by EB.

Data extraction and management

Two review authors (JM and VM) checked the data extraction and resolved any discrepancies or uncertainties by discussion or clarification with the principal investigator. We aimed to extract the number of participants originally allocated to each treatment group in each trial to allow an intention-to-treat analysis if the trial had not already been presented in this way.

Assessment of risk of bias in included studies

We assessed risk of bias as specified in the *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 (March 2011), Chapter 8 (Higgins 2011). We assessed whether the method of randomisation would allow allocation concealment, the adequacy of efforts to blind treatment administration and outcome assessment. For each included trial we collected information about:

- the method of randomisation (including information on allocation concealment);
- blinding of treatment administration;
- blinding of outcome assessment; and
- whether an intention-to-treat analysis was done, or could possibly be done.

We provide detailed 'Risk of bias' tables for the trial included since the last update.

Measures of treatment effect

We extracted the number of participants in the treated and control groups who had:

- died within the first seven to 10 days;
- developed any intracranial haemorrhages, symptomatic or fatal intracranial haemorrhage early after the stroke (within the first seven to 10 days);
- developed symptomatic (including fatal) infarct swelling;
- died by the end of the trial follow-up; and
- were dependent on others in activities of daily living (mRS 3 to 5) by the end of the trial follow-up period (the converse is the number who were alive and independent at the end of follow-up).

We also extracted data to perform subgroup analyses on time to treatment, age, stroke severity, prior or concomitant antithrombotic drug use, and attempted to find information on pretreatment brain imaging findings, blood pressure, and diabetes (details below).

Unit of analysis issues

Our definition of SICH included people who died or deteriorated clinically as a result of intracranial haemorrhage. This could be either secondary bleeding into the infarct or new bleeding at an anatomically separate site elsewhere in the brain or its surrounding spaces after randomisation, confirmed by CT or MR scanning or post-mortem examination. We have defined 'early after the stroke' as within the first seven to 10 days, as the trials each tended to use a slightly different time point, but all had collected information on intracranial haemorrhage certainly within the first 10 days. Many symptomatic haemorrhages actually occurred within the first few days of the stroke. It is difficult to estimate the exact number of SICHs because some people died without a CT scan or post-mortem examination. Thus the true number with SICH may be higher than that suggested by these data. On the other hand, heightened awareness of an association between haemorrhagic transformation and thrombolysis may mean that the investigators too readily attributed any neurological deterioration following treatment to intracranial haemorrhage, even if the amount of blood was small. A review of published CT findings suggests that, at least for some trials, SICH included people with very large swollen and oedematous infarcts with trivial amounts of haemorrhage within them (ECASS 1995; NINDS 1995). Therefore, it is also possible that the risk of intracranial haemorrhage has been overestimated (Von Kummer 2002). The ECASS trial (ECASS 1995) did not report the number with SICH, but whether the radiological appearance of the haemorrhage suggested haemorrhagic transformation of an infarct or parenchymatous haematoma (and its size). Most parenchymatous haemorrhages were associated with symptoms, so we used the number of participants with parenchymatous haematoma as the number with symptomatic haemorrhages.

Dealing with missing data

We contacted trial investigators to obtain all unpublished missing data where possible. Where data were still missing or had not been collected in the original trial, then that trial did not contribute to the relevant outcome. We clarified missing or unclear data with the principal investigator. The outcomes in two studies were very clearly described in the original texts and verification with the principal investigators was not necessary (Haley 1993; Morris 1995).

Assessment of heterogeneity

We tested for heterogeneity between trial results using the I^2 statistic. Heterogeneity might arise from a wide variety of factors, such as the design of the trials, the type of participants included, the use of concomitant treatments like aspirin or heparin, ancillary care during the acute treatment period or rehabilitation, lack of availability of certain data for a particular trial so that a trial appears as missing for a particular outcome, or simply by the play of chance, particularly in small trials (Deeks 2001; Higgins 2003).

Assessment of reporting biases

We have endeavoured to include data from all trials on all prespecified outcomes, obtained from secondary publications or

the trial investigators if unpublished. We assessed the likelihood of missing trials using a funnel plot.

Data synthesis

We calculated odds ratios (ORs) for each outcome (that is, the ratio of the odds of an unfavourable outcome among treatment-allocated participants to the corresponding odds amongst controls), which we calculated using the Peto fixed-effect method (APT 1994), and the random-effects method for outcomes if there was significant heterogeneity between trials. We calculated absolute numbers of events avoided (or caused) per 1000 patients treated using the risk differences method provided in the Review Manager 5 software (RevMan 2012) and also as the straight percentages calculated from the number of events per number randomised in the treated and control groups. However, please note that these events per 1000 treated data should be regarded with caution as they may produce misleading results, since the absolute risk amongst controls varies between trials.

Subgroup analysis and investigation of heterogeneity

We examined the effect of stroke severity, age under or over 80 years, time from stroke to treatment and the effect of having a large infarct on plain CT (ASPECT score 7 or less) on outcome after thrombolysis. We assessed the effect of time by several approaches: we examined the effect of time in all trials regardless of what time windows they contributed to, then in only those trials that contributed to all time windows, and then by latest time to randomisation. These approaches were used to maximise use of available data and minimise bias by excluding some trials from some analyses (e.g. the NINDS 1995 trial only recruited participants up to three hours and therefore would not contribute to an analysis comparing treatment administered within three hours with that administered between three and six hours, where inclusion was restricted to trials which included participants in both time windows). We used the proportion who died in the control group to estimate the severity of stroke. We assessed:

- effect of time to treatment; the number of participants who had symptomatic intracranial haemorrhage, died or were dependent at the end of follow-up according to whether they had been treated within three hours of the stroke or later than three hours (in trials which randomised participants beyond three hours after the stroke);
- the number of participants aged over or under 80 years who had symptomatic intracranial haemorrhage, died or were dependent at the end of follow-up;
- the number of participants who were dead or dependent at the end of follow-up according to whether they had been assessed for inclusion in a trial using CT scanning or MR diffusion- and perfusion-weighted imaging (DWI/PWI);
- the number of participants alive and independent (mRS 0 to 1) at end of follow-up according to whether they had visible or not-visible or small or large infarction on plain CT, measured by the ASPECT score.

Sensitivity analysis

We examined primarily the effect of the thrombolytic drug in all studies for all drugs combined. However, we also examined the effect of different thrombolytic drugs (streptokinase, urokinase, rt-PA). We assessed whether the effect of thrombolysis on functional outcome varied with the definition of dependency (mRS 2 to 5, instead of 3 to 5). Additionally, we compared trials which included participants on the basis of plain CT scanning versus those which used diffusion/perfusion MR imaging or perfusion/angiography CT imaging. We stratified trials by the proportion of participants given aspirin or heparin within the treatment period by time after stroke;

RESULTS

Description of studies

Results of the search

The search of the Cochrane Stroke Group Trials Register identified 19 potentially relevant new or ongoing trials, of which only one was completed and relevant (IST3 2012). Five trials are ongoing (DIAS-3; DIAS-4; DIAS-J; EXTEND; WAKE-UP 2011). Three trials are awaiting classification (FRALYSE; Lin 2006; TESPI): TESPI has recently been completed but not yet reported, and the other two are thought to have been completed but have not yet been published. The remainder of the publications were not relevant. The search of MEDLINE and EMBASE identified 3958 references, which included many additional publications to trials that were already in the review, and several that were relevant to another review (Wardlaw 2013), but none that was relevant to this review.

Included studies

We include 27 trials, involving 10,239 randomised participants, but data for only 10,187 participants were available for inclusion in the review (Abe 1981; ASK 1996; Atarashi 1985; ATLANTIS A 2000; ATLANTIS B 1999; AUST 2005; Chen 2000; DEDAS 2006; DIAS 2005; DIAS 2 2008; ECASS 1995; ECASS II 1998; ECASS 3 2008; EPITHET 2008; Haley 1993; IST3 2012; JTSG 1993; MAST-E 1996; MAST-I 1995; MELT 2007; Mori 1992; Morris 1995; NINDS 1995; Ohtomo 1985; PROACT 1998; PROACT 2 1999; Wang 2003). This review includes all possible available information about all trials in an effort to provide as complete a record as possible of the available data on thrombolysis for acute ischaemic stroke. The NINDS trial (NINDS 1995) was conducted in two consecutive parts, A and B, but published in one paper, so is included as one trial in this review. Although the USA Food and Drug Administration review of the primary analysis of the NINDS trial referred to an 'on-treatment' analysis, the analysis was actually 'intention-to-treat' as no participants who had been entered into the trial were excluded from that analysis (NINDS 1995). Reasons for these comments and further analyses are provided in the Clinical Reviews submitted by Genentech to the USA Food and Drug administration in support of the license application for alteplase (www.fda.gov/cder/biologics/products/altegen061896.htm; see Clinical Review 2, pages 18 to 20).

The trials performed in the 1980s (Abe 1981; Atarashi 1985; Ohtomo 1985) were methodologically different to the trials performed from the 1990s onwards. The 1980s trials used very low doses of thrombolytic drug, given daily intravenously for several days, and started up to five or 14 days after the stroke. The trials from the 1990s onwards used a single large dose of thrombolytic drug (in the region of 80 mg to 100 mg rt-PA or equivalent), given intravenously or intra-arterially, in most trials, within three, six, nine or 24 hours of the stroke. The 1980s trials did not collect data on functional outcome and therefore only the 1990s-onwards trials contribute to the analysis of death or dependency. All trials, however, contributed to analyses of intracranial haemorrhage and death by the end of follow-up (although very few deaths or

intracranial haemorrhages occurred in the trials in the 1980s). However, it is possible to see in the figures what effect the exclusion of these early trials would have on the overall results.

The MAST-I trial (MAST-I 1995), which tested intravenous streptokinase and oral aspirin given within six hours of stroke onset in a two-by-two factorial design, is the only trial to have tested for an interaction between thrombolytic and antithrombotic drugs in a randomised trial; the comparison of streptokinase plus aspirin versus aspirin from MAST-I 1995 is included in this review (separated from the MAST-I 1995 data in the absence of aspirin) because it represents the only available randomised evidence on this important interaction. As there was a significant adverse interaction between streptokinase and aspirin, which we felt was important to highlight, the data for the participants receiving streptokinase in the presence or absence of aspirin are presented separately (that is, streptokinase versus control separate from streptokinase with aspirin versus aspirin). It would not be methodologically appropriate to exclude MAST-I 1995 participants allocated aspirin because in most other trials, some antithrombotic agents were used, and while it is possible to identify the proportion of participants in the trial that received antithrombotic treatment, it is not possible to identify and then exclude the individual participants.

Types and severities of strokes included

The selection of participants was based initially on clinical criteria to diagnose the stroke sub-type (cortical versus lacunar versus posterior circulation):

- eight trials randomised all types of ischaemic stroke: cortical, lacunar and posterior circulation (ATLANTIS A 2000; ATLANTIS B 1999; ECASS 3 2008; Haley 1993; IST3 2012; MAST-I 1995; NINDS 1995; Wang 2003);
- two trials included cortical and lacunar strokes (ASK 1996; Chen 2000);
- five trials included only participants with symptoms of hemispheric cortical ischaemia (ECASS 1995; ECASS II 1998; EPITHET 2008; MAST-E 1996; Morris 1995);
- six trials included participants with angiographically proven occlusion of the internal carotid or middle cerebral artery (JTSG 1993; MELT 2007; Mori 1992; PROACT 1998; PROACT 2 1999) or vertebrobasilar arteries (AUST 2005);
- three trials included presumed 'thrombotic' stroke of most severities and excluded presumed cardio-embolic strokes (although it is not clear whether artery-to-artery embolism counted as 'embolic' in this context) (Abe 1981; Atarashi 1985; Ohtomo 1985);
- three trials included participants with 'tissue at risk' as identified by MR DWI/PWI or CT perfusion imaging (DEDAS 2006; DIAS 2005; DIAS 2 2008).

Most trials used a stroke severity scale, such as the National Institutes of Health Stroke Scale (NIHSS) or Scandinavian Stroke Scale (SSS) or developed their own neurological stroke severity scale to measure the severity of the stroke at baseline.

All trials excluded people who were in a coma; most trials did not randomise many participants who were drowsy except one (MAST-E 1996) in which 50% of the participants were drowsy or stuporous at randomisation.

Age of included participants

- Only seven trials had no upper age limit at all and included also very elderly participants (Abe 1981; Atarashi 1985; EPITHET 2008; IST3 2012; MAST-E 1996; MAST-I 1995; Ohtomo 1985). EPITHET included 25 participants aged over 80 years and IST-3 included 1617 participants aged over 80 years.
- Seven trials had an upper age limit of 85 years (ASK 1996; AUST 2005; DEDAS 2006; DIAS 2005; DIAS 2 2008; PROACT 1998; PROACT 2 1999).
- The NINDS trial (NINDS 1995) initial protocol stated an upper age limit of 80 years. However, this was removed after 188 participants had been recruited into Part A of the trial on 30 March 1992, and thereafter 69 participants over the age of 80 were randomised (the oldest participant was 90) (www.fda.gov/cber/products/altegen061896.htm; Clinical Review 2, page 27).
- All the remaining trials, including all the other rt-PA trials, (except EPITHET 2008; and IST3 2012), had an upper age limit of 80 years.
- The upper age limit in two trials (Chen 2000; MELT 2007) was 75 years.

Visible infarction on the CT scan at randomisation

- Three trials specified that the pre-randomisation CT had to be normal (JTSG 1993; MELT 2007; Mori 1992).
- One trial excluded people with early visible infarction (Wang 2003).
- Six trials specified that the pre-randomisation CT scan had to be normal or only show ischaemic changes in less than one-third of the middle cerebral artery supply territory (ATLANTIS B 1999; ECASS 1995; ECASS II 1998; ECASS 3 2008; EPITHET 2008; Wang 2003).
- Two trials excluded people with mass effect and midline shift on CT (PROACT 1998; PROACT 2 1999).
- None of the other trials specified that people with a CT scan that showed an infarct (which was likely to be symptomatic) should be excluded, although individual doctors may have excluded these individuals in some centres depending on local opinion.
- Three trials selected participants with 'tissue at risk' on the basis of DWI/PWI (DEDAS 2006; DIAS 2005), or MR DWI/PWI or CT with CT perfusion imaging (DIAS 2 2008).

Time to randomisation

The maximum time interval allowed between the onset of the stroke and the start of the treatment administration varied from within three hours to up to two weeks.

- Two trials randomised participants within three hours (Haley 1993; NINDS 1995).
- One trial randomised participants within four hours (ASK 1996).
- One trial randomised participants between three hours and 4.5 hours (ECASS 3 2008).
- One trial randomised participants between three hours and five hours (ATLANTIS B 1999).
- 14 trials randomised participants within six hours (ATLANTIS A 2000; Chen 2000; ECASS 1995; ECASS II 1998; IST3 2012; JTSG 1993; MAST-E 1996; MAST-I 1995; MELT 2007; Mori 1992; Morris 1995; PROACT 1998; PROACT 2 1999; Wang 2003). However, please note that in three studies (MELT 2007; PROACT 1998;

PROACT 2 1999), the majority of the participants were actually randomised between three and six hours.

- One trial randomised participants within three to six hours (EPITHET 2008).
- Three trials randomised participants between three and nine hours (DEDAS 2006; DIAS 2005; DIAS 2 2008).
- One trial randomised participants within 24 hours (AUST 2005).
- Two trials randomised participants within five days (Atarashi 1985; Ohtomo 1985).
- One trial randomised participants within two weeks (Abe 1981).

Please note that the latter three trials (Abe 1981; Atarashi 1985; Ohtomo 1985) do not contribute data to the analysis of early deaths or of death and dependency, as early deaths were not recorded and a functional outcome measure was not used in these trials. They do contribute data to the analyses of intracranial haemorrhages and deaths by the end of follow-up.

Drug and dosage

Trials using intravenous rt-PA contribute 7012 of the 10,187 participants, that is, 69% of the data in this review. Data and outcomes of all included substances are reported for completeness. However, rt-PA data are also given as appropriate.

- Four trials used streptokinase (ASK 1996; MAST-E 1996; MAST-I 1995, Morris 1995).
- Twelve trials used recombinant tissue plasminogen activator (rt-PA) (ATLANTIS A 2000; ATLANTIS B 1999; ECASS 1995; ECASS II 1998; ECASS 3 2008; EPITHET 2008; Haley 1993; IST3 2012; JTSG 1993; Mori 1992; NINDS 1995; Wang 2003).
- Six used urokinase (UK) (Abe 1981; Atarashi 1985; AUST 2005; Chen 2000; MELT 2007; Ohtomo 1985).
- Two used pro-urokinase (pro-UK) (PROACT 1998; PROACT 2 1999).
- Three used desmoteplase (DEDAS 2006; DIAS 2005; DIAS 2 2008).

The mode of administration was intravenous in most trials.

- In all except four of the above trials, the thrombolytic agent was administered intravenously.
  - In two studies (AUST 2005; MELT 2007) the thrombolytic agent was given intra-arterially into the cerebral circulation.
  - Two studies used recombinant pro-urokinase (rpro-UK) given intra-arterially into the cerebral circulation (PROACT 1998; PROACT 2 1999).

Please note that trials testing lumbrokinase did not meet the inclusion criteria for this review. Ongoing trials are testing other new thrombolytic agents such as microplasmin or tenecteplase (see Characteristics of studies awaiting classification and Characteristics of ongoing studies).

The doses were:

- the streptokinase dose was 1.5 MU (as used to treat acute myocardial infarction) in four studies (ASK 1996; MAST-E 1996; MAST-I 1995; Morris 1995);
- the rt-PA dose was similar to that used to treat acute myocardial infarction at 1.1 mg/kg to a maximum of 100 mg in one study (ECASS 1995); about 20% less at 0.9 mg/kg to a maximum of 90 mg in eight studies (ATLANTIS A 2000; ATLANTIS B 1999; ECASS II 1998; ECASS 3 2008; EPITHET 2008; Haley 1993; IST3 2012; NINDS 1995); either 0.7 or 0.9 mg/kg in one study (Wang 2003); and about one-third of 0.9 mg/kg in two studies (JTSG 1993; Mori 1992). All streptokinase and rt-PA doses were administered by intravenous infusion through a peripheral arm vein, over one hour.
- the urokinase dose in the Chinese UK trial (Chen 2000) was 1.5 or 1.0 MU intravenously over 30 minutes (considered to be similar to that used to treat acute myocardial infarction); in three studies (Abe 1981; Atarashi 1985; Ohtomo 1985) the urokinase dose was much lower than the equivalent for acute myocardial infarction and was administered intravenously once daily for seven days. The intra-arterial urokinase dose in one study (AUST 2005) was up to 1.0 MU maximum and in another study (MELT 2007) was up to 60,000 IU;
- the rpro-UK dose was 6 mg in PROACT 1998 and 9 mg in PROACT 2 1999: in both trials it was given intra-arterially, through a catheter with its tip embedded in the occluding thrombus;
- the dose of desmoteplase was 62.5 μ/kg, 90 μ/kg or 125 μ/kg in one study (DIAS 2005), and 90 μ/kg or 125 μ/kg in two studies (DEDAS 2006; DIAS 2 2008).

Concomitant use of antithrombotic treatment

One trial (MAST-I 1995) compared streptokinase versus control among participants who were either allocated to aspirin, or allocated to no aspirin, started within six hours of stroke onset, in a factorial randomisation (in the groups randomised to receive aspirin, it was continued for 10 days).

Antithrombotic use was not randomly assigned in any other trial and its permitted use varied:

- in one study ASK 1996) all participants were to receive 300 mg aspirin starting within four hours of the streptokinase infusion and continued daily thereafter;
- in one study (PROACT 1998) all participants were to receive 1000 u/hour intravenous heparin during the trial angiogram, reduced to 500 u/hour halfway through the trial;
- in one study (PROACT 2 1999) all participants were to receive intravenous heparin 500 u/hour for four hours starting at the time of the angiogram infusion;
- in one study (AUST 2005) all participants received 5000 IU heparin intra-arterially followed by intravenous heparin to a target activated partial thromboplastin time (APTT) of 60 to 80 seconds for a minimum of two days followed by oral warfarin to a target international normalised ratio (INR) of 1.5 to 2.5 for six months;
- in one study (MAST-E 1996) aspirin and intravenous heparin were allowed to start at any time and continue for any time (about 25% of participants received aspirin or heparin within 24 hours and 75% within the first week of the stroke);
- in three studies (ECASS 1995; ECASS II 1998; ECASS 3 2008) subcutaneous heparin was allowed within 24 hours of the stroke (and thereafter) and aspirin after 24 hours (in ECASS II 1998, about 20% of participants were taking aspirin at the time of their stroke and 54% of rt-PA-treated participants received subcutaneous heparin within the first 24 hours, but we are unsure of the corresponding numbers for ECASS 1995, or ECASS 3 2008, nor how many participants in either trial received aspirin or heparin after 24 hours);

- in one study (Haley 1993) a few participants received antithrombotic drugs within 24 hours and thereafter;
- in 10 studies (ATLANTIS A 2000; ATLANTIS B 1999; Chen 2000; DEDAS 2006; DIAS 2005; DIAS 2 2008; IST3 2012; MELT 2007; Mori 1992; NINDS 1995) no antithrombotic drugs were allowed within 24 hours but aspirin was allowed thereafter;
- in three studies (Abe 1981; Atarashi 1985; Ohtomo 1985) antithrombotic drugs were not allowed during the seven days of treatment infusion, but could be used thereafter;
- the antithrombotic drug use is not stated clearly three studies (EPITHET 2008; JTSG 1993; Morris 1995).

Follow-up

Early outcome assessments were made at around seven to 10 days in most trials. Some trials also performed more frequent assessments in the first few hours and days after the trial treatment. In this review, outcome events occurring within the first seven to 10 days (whichever was the later date at which data were collected) have been used to determine the effect of thrombolytic therapy on early outcome.

The final outcome assessment was at:

- about one month after the stroke (Abe 1981; Atarashi 1985; JTSG 1993; Mori 1992; Morris 1995; Ohtomo 1985);
- three months after the stroke (ASK 1996; ATLANTIS A 2000; ATLANTIS B 1999; Chen 2000; DEDAS 2006; DIAS 2005; DIAS 2 2008; ECASS 1995; ECASS II 1998; ECASS 3 2008; EPITHET 2008; Haley 1993; MELT 2007; NINDS 1995; PROACT 1998; PROACT 2 1999; Wang 2003); and
- six months after the stroke (AUST 2005; IST3 2012; MAST-E 1996; MAST-I 1995).

Please note that follow-up at six months and one year have subsequently been reported for one study (NINDS 1995), but the three-month outcome, the primary outcome originally reported, is used in this review. This also occurred in another study (IST3 2012) where the primary six-month outcome originally reported is used, even if the 18-month follow-up, of a predefined vast majority of participating countries, has been subsequently reported.

Please note that because of the difficulty of blinding the biological effect of thrombolytic therapy, it is important to ensure that outcome assessment is blinded and objective. Follow-up should therefore be performed by individuals unaware of the trial treatment allocation either because they have not been involved in the administration of the trial treatment, or in the care of the participant during at least the first few days. In one study (MAST-I 1995) the six-month follow-up was by telephone by a trained observer blind to the treatment allocation. In another study (IST3 2012) the six-month follow-up was blinded and performed either by postal mail or telephone by a trained observer blind to the treatment allocation. Seven studies (ASK 1996; DEDAS 2006; DIAS 2005; DIAS 2 2008; EPITHET 2008; MAST-E 1996; Wang 2003) did not specify who performed the follow-up or that they should not have been involved in the trial treatment administration or participant care in the first 24 hours. In five studies (ATLANTIS A 2000; ATLANTIS B 1999; Chen 2000; ECASS 3 2008; NINDS 1995), follow-up at all stages was done by a doctor who had not been involved in the randomisation or care of the participant in the first 24 hours. In four studies (ECASS 1995; ECASS II 1998; PROACT 1998; PROACT 2 1999), follow-up was by a mixture of individuals; if possible, by someone who had not been involved in the participant's care within the first 24 hours but this may not always have been the case.

Assessment of functional outcome

The assessment of functional outcome was by:

- the Barthel Scale in four studies (ASK 1996; JTSG 1993; Mori 1992; Morris 1995);
- an undefined scale (no, mild, moderate or severe 'limitation') in one study (Haley 1993);
- the Rankin Scale in two studies (MAST-E 1996; MAST-I 1995);
- the modified Rankin Scale in 16 studies (ATLANTIS A 2000; ATLANTIS B 1999; AUST 2005; Chen 2000; DEDAS 2006; DIAS 2005; DIAS 2 2008; ECASS 1995; ECASS II 1998; ECASS 3 2008; EPITHET 2008; MELT 2007; NINDS 1995; PROACT 1998; PROACT 2 1999; Wang 2003);
- the Oxford Handicap Scale (OHS), a commonly used variant of the modified Rankin score, was used in one study (IST3 2012);
- it was not assessed in three studies (Abe 1981; Atarashi 1985; Ohtomo 1985).

Some trials used more than one scale to measure outcome; for example, six studies (ATLANTIS A 2000; ATLANTIS B 1999; DEDAS 2006; DIAS 2005; DIAS 2 2008; NINDS 1995) favoured a 'Global Outcome Statistic' which involved collecting Barthel, Rankin, Glasgow Outcome Score and NIHSS scores individually and then combining the four scores. Three trials (Abe 1981; Atarashi 1985; Ohtomo 1985) used the 'Global Improvement Rating', which measures change in neurological status and safety outcome as a composite surrogate for functional outcome.

There are differences in the primary outcome measure used between trials, in that some used a 'poor functional outcome' and some used a 'good outcome'. The following trials sought 'dependency' (that is, whether the participant was dependent or not in activities of daily living) as a measure of poor functional outcome: two studies (MAST-E 1996; MAST-I 1995) defined dependency as Rankin 3 or worse, and two studies (ASK 1996; Morris 1995) defined dependency as a Barthel score of 60 or worse. In one study (IST3 2012) 'alive and independent' (OHS 0 to 2; mRS 0 to 2) was the primary measure of outcome. The 'alive and favourable outcome' (mRS 0 to 1) and ordinal analysis were included in prespecified secondary outcome analyses.

Thirteen trials sought 'good functional outcome' (that is, whether the participant had made a complete or virtually complete recovery) defining 'good outcome' as mRS 0 or 1 (ATLANTIS A 2000; ATLANTIS B 1999; Chen 2000; DEDAS 2006; DIAS 2005; DIAS 2 2008; ECASS 1995; ECASS II 1998; ECASS 3 2008; EPITHET 2008; MELT 2007; NINDS 1995; Wang 2003).

For most trials, it has been possible to obtain data on participants in each individual Rankin (or Barthel) group, or data dichotomised on Rankin 0 to 2 versus 3 to 6, or 0 to 1 versus 2 to 6, so that dependency in this review refers to Rankin, (mRS or OHS) 3 to 5 (6 being dead) unless otherwise stated. There are only two trials for which the number of participants in individual Rankin groups is not so far available (and therefore the data shown are for Rankin 2 or worse) (ATLANTIS A 2000; PROACT 1998).

Excluded studies

We excluded two trials conducted prior to the availability of CT scanning (Meyer 1963; Meyer 1964) as there was no way of confirming that the stroke was ischaemic. One small trial of intra-arterial streptokinase stopped prematurely after four participants had been randomised due to the impracticality of the intra-arterial technique (Edinburgh 1991). A trial started in Hong Kong was abandoned after a few participants had been randomised because of concerns that streptokinase might cause too many haemorrhages (Hong Kong 1994) (two trials (ASK 1996; MAST-E 1996) had both just stopped prematurely creating an adverse climate for the conduct of trials testing streptokinase). We excluded one trial (Naito 1984) after discussion with Professor T Abe (co-investigator) as it was not possible to account for 11 of the 101 randomised participants (most of whom were in the control group). We excluded six trials conducted in China, two because of confounding (Xiang 1995; Yuan 1995), one because the duration of follow-up was only three weeks (Pang 1993), two that evaluated oral lumbrokinase thrice daily for 21 days but within an unspecified time window and without clinical outcome assessment (Jin Urokinase metaanalysis 2000; Huang 2000), and one that assessed ahylysantifarctase but lacked clinical outcomes (Liu 1994). A further 73 trials have also been excluded due to a range of reasons given in the Characteristics of excluded studies table. Studies that were potentially relevant but were confounded are listed in the Characteristics of excluded studies table and the reason given.

Risk of bias in included studies

We have included 27 trials: six trials using intravenous thrombolytic therapy published prior to 1995, 17 trials from 1995 to 2012, and four trials using intra-arterial thrombolytic therapy.

Allocation

Among the included studies 14 (52%) fulfilled criteria for high grade concealment. The concealment has successively improved over time with the development and utilisation of new randomisation methods, such as the use of a centralised computerised method with interactive interface for randomisation over the telephone or Internet.

- Twelve trials used central telephone or Internet randomisation (ASK 1996; AUST 2005; DEDAS 2006; DIAS 2005; DIAS 2 2008; ECASS 3 2008; IST3 2012; MAST-E 1996; MAST-I 1995; MELT 2007; PROACT 1998; PROACT 2 1999). In five studies (AUST 2005; IST3 2012, MAST-I 1995; MELT 2007; PROACT 2 1999), the allocated treatment was then given unblinded without a placebo. In one of the studies (IST3 2012) with the exception of 276 participants treated in the double-blinded phase of the trial, the remaining participants (2759) were treated unblinded without placebo. In four other studies (ASK 1996; ECASS 3 2008; MAST-E 1996; PROACT 1998) sealed prepacks of thrombolytic drug or identical-appearing placebo were given according to the randomisation instructions.
- In three trials randomisation was at the participating hospital by selection of a sealed, sequentially-numbered, prepack (of active drug or identical appearing placebo) followed within two hours by a telephone call to the Central Trial Co-ordinating Office to notify them of the participant and the number of the drug pack (ATLANTIS A 2000; ATLANTIS B 1999; NINDS 1995). In one study (NINDS 1995), the randomisation system, set up in an effort to reduce delays to treatment, led to 'out of order' trial treatment allocations in between 13 and 31 participants, which affected every subsequent participant until the error was detected, and led to participants appearing to cross between treatment allocations (more moved from rt-PA to placebo than the other way round). Also in the interests of reducing delays to trial treatment administration, there were some participants who ultimately were not entered into the study after the pharmacy had prepared the trial pack (and therefore some discarded trial packs). Details of the randomisation are given at www.fda.gov/cber/products/altegen061896.htm; *see* Clinical Review 2, page 11-12 and 18-19.
- In three trials, randomisation was by selection of a sequentially numbered, sealed drug prepack at the participating centre provided by the sponsor from a randomisation schedule drawn up centrally (ECASS 1995; ECASS II 1998; EPITHET 2008).

Of the remaining trials:

- five trials used sealed drug prepacks of active drug or identical-appearing placebo (Abe 1981; Atarashi 1985; JTSG 1993; Mori 1992; Ohtomo 1985);
- one used sealed envelopes (Haley 1993);
- one used sealed drug prepacks of active drug or normal saline (as placebo) (Chen 2000);
- the method was not stated in two (Morris 1995; Wang 2003).

Please note that, therefore, only two of the rt-PA trials (ECASS 3 2008: IST3 2012) recorded the participant details centrally over the telephone or Internet prior to starting trial treatment. In one of these trials (IST3 2012) a minimisation algorithm was used to balance the study arms for key prognostic variables like stroke severity before randomisation. Several later studies have made use of modern randomisation techniques and entering key prognostic variables into the IT system before randomisation, which allows balancing of the study arms - as has been introduced in one trial (IST3 2012) .

Blinding

Five trials were single-blind without a placebo (AUST 2005; MAST-I 1995; MELT 2007; PROACT 2 1999; Wang 2003). In one trial (IST3 2012) the first 276 participants were treated in the double-blinded phase of the trial and all 2759 remaining participants were included into the open phase of the trial. All participants in the study, irrespective of study phase, were blindly assessed by postal mail or telephone by a blinded and trained observer. In PROACT 2 1999, the control group underwent catheter placement but received no infusion. All the rest were double-blind placebo-controlled trials. However, it should also be noted that thrombolysis, due to its effects on the coagulation system at high doses, can be difficult to blind completely due to the obvious signs of bleeding (prolonged bleeding at venepuncture sites, easy bruising, gingival or conjunctival haemorrhages, etc). Thus, provision of an identical-appearing placebo (in the syringe) may not fully blind investigators to treatment allocation. Furthermore, as thrombolytic agents are proteins, they froth when shaken in solution with water or saline, rather like egg white mixed with water and shaken. Normal saline is therefore not an identical-looking placebo for a thrombolytic agent. Thus, in addition to the possibilities for failure of treatment allocation concealment inherent in the randomisation methods

used as outlined above, it is possible that treatment allocation could be guessed accurately by the physicians caring for the participant in the acute phase because of these biological effects. Accordingly, methods for ensuring complete blinding of treatment allocation at late follow-up are crucial. Only one study (MAST-I 1995) used central telephone follow-up by a blinded trained observer. Although seven other trials specified that follow-up was to be by a physician not involved in the acute care of the participant, it is uncertain how completely this was achieved in practice. Other trials either did not specify who should do the follow-up, or did not make it mandatory that follow-up was by an independent physician, so in either case follow-up may have been carried out by the acute phase physician who could have been influenced by their knowledge of events in the acute phase.

Incomplete outcome data

All available data are included. Data on six participants were missing from the ATLANTIS B 1999 trial publication and details have not been forthcoming from the investigators, and we have not yet received data on 46 participants from the Chinese UK Trial (Chen 2000) (these participants were randomised after the trial's six-hour time limit and have not yet been supplied). More information is available for some trials than for others, either because the trial collaborators have published very actively on various aspects of their trial, or because in some cases further information is available from other sources (for example, reports on NINDS 1995 appear on the US Food and Drug Administration (FDA) website as part of the licence application process). The more frequent reporting or greater completeness of the data for some trials is merely a reflection that more information is available for those trials, and not intended to over- or under-emphasise the actual results or quality of any particular trial (or trials) compared with others for which there is less detailed information available.

Selective reporting

We have avoided, as far as possible, any reporting bias by obtaining original data from the trial investigators where these have not been published. Only the intention-to-treat results are included here. In any trials where there have been exclusions, these were made prior to the breaking of the randomisation code. A strict intention-to-treat analysis was used in 18 studies (ASK 1996; ATLANTIS A 2000; ATLANTIS B 1999; AUST 2005; DEDAS 2006; DIAS 2005; DIAS 2 2008; ECASS 1995; ECASS II 1998; ECASS 3 2008; EPITHET 2008; IST3 2012; MAST-E 1996; MAST-I 1995; MELT 2007; PROACT 1998; PROACT 2 1999; Wang 2003), but not in any of the earlier trials. The administrative problems with randomisation in one study (NINDS 1995) led the FDA reviewer to describe the primary analysis as an 'on-treatment analysis'. However, the primary analysis was undertaken without excluding any participants entered into the trial and was, therefore, an intention-to-treat analysis (www.fda.gov/cber/products/altegen061896.htm; *see* Clinical Review 2, page 20). For the earlier trials, with additional information from the principal investigators if necessary, we have attempted to find a final outcome for all randomised participants, rather than simply relying on the published data from which some randomised participants may have been excluded. Note that one trial (ECASS 1995) was published as intention-to-treat and as a 'target population' after about 20% of the randomised participants had been excluded, but only the intention-to-treat data have been included here.

Other potential sources of bias

Randomisation in two trials, ASK 1996 (in the over-three-hour group) and MAST-E 1996, was stopped on the advice of their respective data monitoring committees after only about half of the originally intended number of participants had been randomised. One study (MAST-I 1995) was suspended by its steering committee (in view of the stopping of MAST-E 1996 and ASK 1996) to examine its interim results after randomising about one third of its originally intended number. Another study (MELT 2007) was discontinued on the advice of its data monitoring committee when rt-PA was licensed in Japan in 2005. Another study (AUST 2005) was discontinued on the basis of very slow recruitment after 24 participants of a planned sample of 200 had been included. Four studies (ECASS 1995; ECASS II 1998; NINDS 1995; PROACT 2 1999) all reached their planned targets. One study (PROACT 1998) was stopped after completing two of its planned three dosage arms by the pharmaceutical provider. Another study (ATLANTIS A 2000) was stopped on publication of the NINDS 1995 trial, and continued in modified form as ATLANTIS B 1999, which in turn stopped in 1998 following a 'futility analysis' prompted by results from the ECASS II 1998 study. Examination of funnel plots for the main outcomes showed these to be symmetrical and therefore provided little evidence of publication bias.

Effects of interventions

See Data and analyses. Note that in each analysis, trials are grouped by thrombolytic drug and whether intravenous or intra-arterial, with a subtotal odds ratio (OR) for that group. The overall OR for all trials appears at the bottom of each plot. Note that one study (MAST-I 1995) appears twice in the analyses because the data in participants allocated aspirin have been entered separately from the participants allocated no aspirin. Also note that some outcomes have fewer trials contributing data than other outcomes. This is because not all trials collected data on all outcomes examined in this review, or if they did collect data on the particular outcome, it may not be available. If data were available for a particular outcome, then the trial appears listed in the relevant analysis. The 2012 systematic review and meta-analysis of rt-PA (Wardlaw 2012) conducted a comparison of the 11 earlier rt-PA studies (ATLANTIS A 2000; ATLANTIS B 1999; ECASS 1995; ECASS 3 2008; ECASS II 1998; EPITHET 2008; Haley 1993; JTSG 1993; Mori 1992; NINDS 1995; Wang 2003) and IST3 2012 on its own, and analysed the effect of adding IST-3 to the 11 earlier trials. That analysis is not repeated here.

Deaths from all causes within seven to 10 days

Data on deaths occurring within the first seven to 10 days were available for 13 trials (7458 participants; Analysis 1.1). Amongst the larger and more recently completed trials, data were not available for seven trials (ATLANTIS A 2000; ATLANTIS B 1999; DEDAS 2006; DIAS 2005; NINDS 1995; PROACT 1998; PROACT 2 1999). There was a significant excess of early deaths with thrombolysis: 11.5% of those allocated to thrombolytic therapy died compared with 7.4% of those allocated to control (OR 1.69, 95% confidence interval (CI) 1.44 to 1.98, $P < 0.00001$). In absolute terms, if confirmed, this is an increase of 40 (95% CI 30 to 55) early deaths per 1000 participants treated with thrombolysis. There was borderline significant heterogeneity ($I^2 = 41\%$).

Data on early deaths were available for eight trials using intravenous rt-PA. The numerical (tabular) data on early deaths for the NINDS trial (NINDS 1995) have not been published, but the

NINDS trial did publish a survival curve which suggested that fewer deaths occurred in the rt-PA-treated participants from 24 hours after treatment onwards. The tabular data available from the other rt-PA trials showed a significant excess of early deaths: the OR was 1.44 (95% CI 1.18 to 1.76, P = 0.0003; 5535 participants) with no significant heterogeneity; the absolute effect was 25 more (95% CI 11 to 40 more) deaths per 1000 participants treated. In the three trials using streptokinase, there was also a significant excess of early deaths (OR 1.90, 95% CI 1.37 to 2.63; 963 participants).

We also performed an analysis of the data using a random-effects model. This also shows a statistically significant excess of deaths with thrombolysis of similar magnitude to the fixed-effect analysis (all trials: OR 1.68, 95% CI 1.30 to 2.16, P < 0.0001; just trials of rt-PA: OR 1.44 , 95% CI 1.18 to 1.77, P = 0.0004).

Fatal intracranial haemorrhage within seven to 10 days

Data were available from 17 trials on fatal intracranial haemorrhage (9066 participants; Analysis 1.2). There are 10 trials for which this outcome is not currently available (Abe 1981; AUST 2005; DEDAS 2006; DIAS 2005; DIAS 2005; EPITHET 2008; JTSG 1993; Mori 1992; PROACT 2 1999; Wang 2003). This outcome may underestimate the frequency of intracranial haemorrhage since some of the participants who died without a post-mortem examination or CT scan may have died of intracranial haemorrhage. There was a significant, approximate six-fold increase in the rate of fatal intracranial haemorrhage with thrombolysis (4.19% of participants allocated to thrombolysis compared with 0.65% of those allocated to control, OR 4.53, 95% CI 3.47 to 5.91, P < 0.00001). There was no statistically significant heterogeneity (I^2 = 0%).

In eight trials using rt-PA, there were 30 (95% CI 20 to 40) extra fatal intracranial haemorrhages per 1000 participants treated (OR 4.18, 95% CI 2.99 to 5.84, P < 0.00001; 6683 participants) with no statistically significant heterogeneity between trials (I^2 = 0%).

The combination of streptokinase with aspirin in one study (MAST-I 1995) significantly increased fatal intracranial haemorrhage (OR 4.56, 95% CI 1.62 to 12.84; 309 participants), and more participants died of cerebral causes without a CT scan or autopsy who may therefore also have had intracranial haemorrhage than in the group who received aspirin alone.

Deaths within the first seven to 10 days from causes other than fatal intracranial haemorrhage

We calculated the effect of thrombolysis on death from causes other than fatal intracranial haemorrhage for the 10 trials that provided data on both early death and fatal intracranial haemorrhage (7226 participants; Analysis 1.3). Note that, unfortunately, this excludes several large trials (ATLANTIS A 2000; ATLANTIS B 1999; DEDAS 2006; DIAS 2005; NINDS 1995; PROACT 1998; PROACT 2 1999), which did not provide data on early death. There were 264/3752 (7.0%) non-intracranial haemorrhage deaths in the thrombolysis-treated participants and 234/3474 (6.7%) in the control participants (OR 1.08, 95% CI 0.90 to 1.30, P = 0.39) with significant between-trial heterogeneity (I^2 = 53%, P = 0.02). In comparison with Analysis 1.2 this suggests that most of the excess in early deaths of 42 per 1000 treated with thrombolysis is attributable to intracranial haemorrhage.

In participants treated with rt-PA (ECASS 1995; ECASS 3 2008; ECASS II 1998; Haley 1993; IST3 2012), 141/2669 (5.2%) died within the first seven to 10 days of causes other than intracranial haemorrhage, compared with 150/2634 (5.7%) in the control group, OR 0.93, 95% CI 0.73 to 1.18, P = 0.54, I^2 = 30%; 5303 participants),

Symptomatic (including fatal) intracranial haemorrhage within seven to 10 days

All trials provided data on intracranial haemorrhage and most provided them in a form that made it clear how many participants had suffered a neurological deterioration associated with the appearance of new haemorrhage in the brain on a CT or MR brain scan or at post-mortem examination (10,186 participants; Analysis 1.4). There was a highly significant four-fold increase in symptomatic intracranial haemorrhage with thrombolysis in 7.5% of those allocated to thrombolysis versus 1.7% of those allocated to control (OR 3.75, 95% CI 3.11 to 4.51, P < 0.00001) with no statistically significant between-trial heterogeneity (P = 0.36). This represents an extra 60 (95% CI 50 to 65) symptomatic intracranial haemorrhages per 1000 participants treated.

In 12 trials using rt-PA, there were 60 (95% CI 50 to 70) extra symptomatic intracranial haemorrhages per 1000 participants treated (OR 3.72, 95% CI 2.98 to 4.64, P < 0.00001; 7011 participants) with no heterogeneity between trials (I^2 = 28%, P = 0.17).

Excluding the trials that used lower doses of thrombolysis and had lower rates of fatal and symptomatic intracranial haemorrhage had little effect on the overall result as they contributed relatively few of the data to this analysis.

Symptomatic (including fatal) cerebral oedema

Six trials all testing rt-PA provided data on symptomatic including fatal infarct swelling (ATLANTIS B 1999; ECASS 1995; ECASS II 1998; ECASS 3 2008; IST3 2012; NINDS 1995) (Analysis 1.5; 5961 participants). There was no overall reduction in symptomatic infarct swelling with thrombolysis: 10.2% of those allocated thrombolysis had symptomatic infarct swelling compared with 10.4% of those allocated control (OR 0.97, 95% CI 0.79 to 1.19, P = 0.75) with significant heterogeneity (I^2 = 71%, P = 0.004). Due to the heterogeneity we undertook an analysis according to a random-effects model. This gave very similar results (OR 0.79, 95% CI 0.62 to 1.51, P = 0.88), and identical heterogeneity compared with the fixed-effect model.

Deaths from all causes during follow-up

Data were available for all 27 trials (10,187 participants) (Analysis 1.8). There was a modest but significant increase in deaths within scheduled follow-up, from 18.0% in controls to 19.4% in the participants allocated to thrombolysis (OR 1.18, 95% CI 1.06 to 1.30 , P < 0.002). In absolute terms, this represented an extra 15 (95% CI six fewer to 30 more) deaths at the end of follow-up per 1000 participants treated with thrombolysis. There was heterogeneity between the trials (I^2 = 48%, P = 0.003) reflected in the fact that some trials (for example, ECASS II 1998; IST3 2012; MAST-I 1995 (of participants allocated to the thrombolytic agent alone) and NINDS 1995) showed a non-significant reduction and others (for example, ASK 1996, ATLANTIS A 2000 and MAST-I 1995 (of participants allocated to the thrombolytic agent plus aspirin)) showed a significant increase in case fatality with thrombolysis.

In the 12 trials using intravenous rt-PA, there was no net effect on deaths (OR 1.06, 95% CI 0.94 to 1.20; 7012 participants) equivalent

overall to seven more (two fewer to 25 more) deaths per 1000 participants treated. The heterogeneity of treatment effect among the trials of rt-PA was not quite statistically significant (I^2 = 38%, P = 0.09).

In view of the statistically significant heterogeneity for all trials (I^2 = 48%), we performed an analysis of the data using a random-effects model. This also shows a statistically significant excess of deaths with thrombolysis of similar magnitude to the fixed-effect analysis (all trials: OR 1.26, 95% CI 1.04 to 1.52 P = 0.02).The results for just trials of rt-PA (OR 1.12, 95% CI 0.90 to 1.38, P = 0.31) were also of similar magnitude as the fixed-effect model and still without any statistical significance.

Deaths occurring between seven and 10 days and the end of follow-up

We examined the number of deaths occurring between the first seven to 10 days and the end of follow-up in the 13 trials that provided data for both early and late deaths (ASK 1996; Chen 2000; DIAS 2 2008; ECASS 1995; ECASS II 1998; ECASS 3 2008; EPITHET 2008; Haley 1993; IST3 2012; MAST-E 1996; MAST-I 1995; Mori 1992; Wang 2003). There were 425/3890 (10.9%) deaths in this period in the thrombolysis-treated participants compared with 460/3568 (12.9%) in the control participants, a difference of 2 per 1000, OR 0.88 (95% CI 0.76, 1.02, P = 0.09; 7458 participants). There was significant heterogeneity (I^2 = 57%, P = 0.007) (Analysis 1.7). In eight trials testing rt-PA, the corresponding OR was 0.84 (95% CI 0.71 to 0.99; 5535 participants) also indicating fewer deaths between seven and 10 days and the end of follow-up. This analysis suggests that most of the deaths that occur following thrombolysis, including rt-PA, occur in the first seven to 10 days, and that thereafter the number of deaths occurring in thrombolysis-treated participants is very similar to that occurring in the control participants, or fewer than in the control group in trials testing rt-PA. IST3 2012 provided data on death at six months, which suggested that the longer duration of follow-up (six instead of three months) allowed for the deaths in the control group occurring after the first seven to 10 days (300/1520, 19.7%, versus 245/1515, 16.2% in rt-PA treated participants) to overtake the excess of deaths due to fatal intracranial haemorrhage after rt-PA occurring in the first seven to 10 days, leading to a net-neutral overall effect on death at long-term follow-up with rt-PA.

Death or dependency at the end of follow-up

Analysable data from 22 trials (including all recently completed and large trials) on functional outcome were available for 9318 participants (Analysis 1.6). Two further trials also assessed functional outcome but the data from one (Haley 1993) were incomplete (3/27 participants were alive but lost to follow-up), and in the other (JTSG 1993) the Barthel Scores were not available.

There was a significant reduction in death or dependency with thrombolysis: 54.8% compared with 58.9% of those allocated to control (OR 0.85, 95% CI 0.78 to 0.93, P = 0.0002). This is equivalent to 41 (95% CI 20 to 60) fewer dead or dependent participants per 1000 treated. There was significant heterogeneity of treatment effect between the trials (I^2 = 39%, P = 0.03).

For the 10 trials using intravenous rt-PA (6886 participants), the OR was 0.84 (95% CI 0.77 to 0.93, P = 0.0006), equivalent to 40 (95% CI 20 to 65) fewer participants being dead or dependent per 1000 treated. There was significant heterogeneity of treatment effect among the trials using rt-PA (I^2 = 63%, P = 0.004).

In view of the statistically significant between-trial heterogeneity, we performed an analysis of the data on death or dependency using a random-effects model. This gives an OR of 0.83 (95% CI 0.73 to 0.95, P = 0.006) for all trials, and of 0.80 (95% CI 0.66 to 0.97, P = 0.03) for just trials of rt-PA. (Note of caution: random-effects analyses place undue weight on smaller studies and possibly should be avoided with combined outcomes. Death and dependency actually reflect two outcomes which may 'pull' in different directions. Small studies may have more extreme results and give less reliable estimates of true treatment effect than large studies).

If an alternative definition of 'poor outcome' (Rankin score 2 to 6) is used in this analysis, and the analysis is restricted to just the 21 trials with both definitions available, then the ORs are as follows:

- mRS 2 to 6 for any thrombolytic drug versus control OR 0.76 (95% CI 0.70 to 0.84, P = 0.00001; 8824 participants) with significant between-trial heterogeneity (I^2 = 45%, P = 0.02); for just rt-PA trials, the OR was 0.79 (95% CI 0.71 to 0.88, P = 0.00001; 6887 participants), but also with significant heterogeneity (I^2 = 64%, P = 0.003) (Analysis 1.9);
- mRS 3 to 6 for any thrombolytic drug versus control OR 0.85 (95% CI 0.78 to 0.93, P = 0.15 with non-significant between-trial heterogeneity (I^2 = 25%; 8824 participants); for 10 just rt-PA trials, the OR was 0.85 (95% CI 0.77 to 0.94, P = 0.001; 6887 participants), and also with borderline significant heterogeneity (I^2 = 47%, P = 0.05) (Analysis 1.10).

Although the confidence intervals for poor outcome defined by mRS 3 to 6 and 2 to 6 overlap for analyses of all thrombolytic drugs and of just rt-PA, these data suggest that choosing mRS 2 to 6 as the primary outcome may provide a more positive trial result. Heterogeneity is present for poor outcome defined as mRS 2 to 6 as for poor outcome defined as mRS 3 to 6. This suggests that none of these dichotomous outcomes is specifically robust and that a more cautious estimate of overall thrombolysis and of rt-PA effect, such as the ordinal shift analysis, is wise. Note that some individual trials 'wobble' from being positive to not positive in going between the mRS definitions (some go one way and some the other) but overall the trend is to more positive results with mRS 2 to 6. For example, ECASS II 1998 was neutral on its primary outcome of mRS 2 to 6, but positive on the alternative outcome of mRS 3 to 6; ECASS 3 2008 was positive on its primary outcome of mRS 2 to 6, but neutral on mRS 3 to 6; NINDS 1995 became less positive on mRS 3 to 6; Wang 2003 moves from very positive on mRS 2 to 6 to neutral on mRS 3 to 6, the latter trial illustrating the particular instability of small and highly positive studies, and IST3 2012 went from neutral on mRS 3 to 6 to positive on mRS 2 to 6 as well as on ordinal shift analysis.

Dependency at the end of follow-up

We examined the effect of thrombolysis on dependency defined as mRS 3 to 5 in the 22 trials with analysable data (9318 participants; Analysis 1.11). There were 1649/4891 (33.7%) dependent participants amongst those treated with thrombolysis and 1761/4427 (39.8%) in the control group, an absolute reduction in dependent participants of 60 per 1000 participants treated with thrombolysis, OR 0.75 (95% CI 0.69 to 0.82, P < 0.00001), with borderline significant between-trial heterogeneity (I^2 = 47%, P = 0.007) or between the groups treated with different thrombolytic

drugs (I^2 = 55%, P = 0.04). This would suggest that amongst those who avoid early death (when most of the excess of deaths attributable to thrombolysis appear to occur), there is a highly significant and worthwhile reduction in the risk of being dependent with any thrombolytic treatment. Amongst those treated with rt-PA, the reduction in dependency was similar, with an OR of 0.80 (95% CI 0.73 to 0.89, P < 0.0001; 6886 participants, 10 trials) but with between-trial heterogeneity (I^2 = 53%, P = 0.02).

Alive and independent at the end of follow-up

We provide data on the number of participants who were alive and independent (mRS 0 to 2) (Analysis 1.12) and alive and with favourable outcome (mRS 0 to 1) (Analysis 1.13) at the end of follow-up for trials testing rt-PA up to six hours after stroke. For mRS 0 to 2, 1611/3483 participants given rt-PA were alive and independent versus 1434/3404 (42%) allocated control, OR 1.17 (95% CI 1.06 to 1.29, P = 0.001; 10 trials, 6887 participants) with significant heterogeneity (I^2 = 47%, P = 0.05). For mRS 0 to 1, 1211/3483 participants allocated rt-PA versus 998/3404 allocated control were alive with a favourable outcome (OR 1.29, 95% CI 1.16 to 1.43, P < 0.00001; 10 trials, 6887 participants) but with significant heterogeneity (I^2 = 57%, P = 0.01).

Possible sources of between-trial heterogeneity

To attempt to identify possible causes for the heterogeneity of the data on death (amongst all trials), functional outcome and symptomatic intracranial haemorrhage (SICH) in rt-PA trials, we have ordered the trials by:

- thrombolytic drug used (in all main outcome analyses);
- concomitant antithrombotic drug usage;
- time to treatment;
- severity of stroke among participants randomised based on the case fatality in the control group (dichotomised on 0% to 19%, and 20% or more)
- use of CT scanning versus MR diffusion- and perfusion-weighted imaging (DWI/PWI) mismatch or CT perfusion prior to inclusion; and
- CT scan ASPECTS score, which is a measure of the extent of acute ischaemic tissue changes.

We have also examined the effect of time to treatment and effect of imaging modality (CT versus MR DWI/PWI mismatch or CT perfusion) on:

- death or dependency;
- alive and independent;
- death by the end of follow-up; and
- SICH.

There are obviously many other possible causes of heterogeneity, but it has not been possible to examine these systematically at the present time. These include, for example, the availability of data, the design of the trials, other aspects of the participant population apart from stroke severity, and the play of chance amongst what are still mainly relatively small trials.

Thrombolytic drug used

The indirect comparisons of the effects of each individual drug on death at the end of follow-up (Analysis 1.8), death or dependency (Analysis 1.6), or SICH (Analysis 1.4) - like all indirect comparisons - are confounded by a number of factors, and hence not reliable. These trials differ in many respects apart from just the thrombolytic drug used, or its dose (for example the dose of streptokinase used in ASK 1996; MAST-E 1996; and MAST-I 1995 was similar to that used in myocardial infarction; a lower dose would perhaps be more relevant to a typical older stroke population). Although trends were observed, there were no statistically significant differences in symptomatic intracranial haemorrhage or death or dependency between trials using urokinase, streptokinase, rt-PA or desmoteplase. There was significant between-trial heterogeneity for death at the end of follow-up (Analysis 1.8). Examination of this analysis shows that the MAST-I streptokinase-plus-aspirin arm is a particular outlier with a large excess of deaths in the participants allocated streptokinase-plus-aspirin; the heterogeneity became non-significant after removal of MAST-I aspirin-plus-streptokinase-allocated participants (I^2 dropped to 28%, P = 0.09). For all outcomes, including death at the end of follow-up, there was considerable overlap between the 95% confidence intervals, clearly indicating that there are other differences between these trials in addition to the drug being tested. For example, the desmoteplase trials included participants as late as nine hours, whereas most other trials only included participants up to six hours. Any apparent differences between drugs may therefore be due to factors other than the drug in question.

Concomitant antithrombotic drug use

It is not possible to comment on the effect of aspirin use prior to the stroke; although some trials recorded prior aspirin use, we could not extract data from the publications in a comparable manner and none of the earlier trials balanced randomisation on prior aspirin use. In IST3 2012 treatment with antiplatelet drugs in the previous 48 hours was consistently collected and included among the pre-randomisation variables. The interaction between thrombolytic drugs and antithrombotic drugs given simultaneously (or the latter very soon after the former) was only tested by random allocation in one study (MAST-I 1995), which therefore provides the only truly valid evidence on this potential interaction. In this study there was a clinically important adverse interaction between aspirin and streptokinase when given simultaneously, resulting in a substantial increase in case fatality (early and late), which was not offset by a reduction in the number of dead or dependent participants by the end of follow-up (28% of those allocated to streptokinase alone versus 43% of those allocated to streptokinase plus aspirin were dead by the end of follow-up (P < 0.001), and 62% and 63% were dead or dependent respectively (versus 68% in the control group)). The actual cause of the increase in early and total deaths with streptokinase and aspirin appears largely to be due to cerebrovascular events. Aspirin with streptokinase significantly increased the number of deaths in hospital from all causes (OR 2.2, 95% CI 1.3 to 3.8), from neurological causes (OR 2.0, 95% CI 1.1 to 3.7), and intracranial haemorrhage on CT scan or at autopsy (OR 2.2, 95% CI 1.0 to 5.0) when compared with the group who received streptokinase alone. There was no difference in deaths from neurological causes without intracranial haemorrhage, but note also that more participants in the streptokinase plus aspirin group died of neurological causes without a CT scan or autopsy, so could also have had an intracranial haemorrhage, that is, the increase in intracranial haemorrhage with aspirin and streptokinase may be even greater (Ciccone 1998).

Information is also available on antithrombotic drug use (although not randomly allocated) in 20 other trials (ASK 1996; ATLANTIS A 2000; ATLANTIS B 1999; AUST 2005; Chen 2000; DEDAS 2006; DIAS 2005; DIAS 2 2008; ECASS 1995; ECASS II 1998; ECASS 3 2008; EPITHET 2008; Haley 1993; IST3 2012; MAST-E 1996; MELT 2007; Mori 1992; NINDS 1995; PROACT 1998; PROACT 2 1999), and some further data in three other trials (Abe 1981; Atarashi 1985; Ohtomo 1985) (9674 participants; Analysis 1.14). The odds of death by the end of follow-up were increased in line with the frequency, the amount, and proximity to the administration of thrombolysis of the concomitant antithrombotic drug use (OR 1.31 when all participants received antithrombotic drugs within 24 hours of thrombolysis; 1.27 when some participants received antithrombotic drugs within 24 hours; 1.13 when no participants received antithrombotic drugs within 24 hours but some thereafter; and 0.89 for no antithrombotic drugs within the first 10 to 14 days; I^2 = 50%, P = 0.002). Although these data are based on non-randomised comparisons, they do support the evidence of a clinically significant adverse interaction between thrombolysis and antithrombotic drugs given concurrently found in the MAST-I 1995 study and may go some way towards explaining the heterogeneity between the trials for case fatality

Severity of stroke among randomised participants

There was no obvious statistically significant difference in the effect of thrombolysis on case fatality between trials with a case fatality rate less than 19% in the control group (OR 1.31, 95% CI 1.08 to 1.58; 17 trials, 4973 participants) and those with a case fatality rate greater than 20% in the control group (OR 1.05, 95% CI 0.92 to 1.19; 10 trials, 4905 participants; pooled I^2 = 28%, P = 0.09) (Analysis 1.15). However, this crude comparison may mask an important relationship between stroke severity and hazard with thrombolysis. Post-hoc statistical correction methods are unlikely to be adequate, so combined individual patient data from published rt-PA trials may be incorrect. Also, unfortunately, analysis based on an outcome in the control group is prone to bias due to regression to the mean (Sharp 1996). Nonetheless, the post-hoc analyses of both the NINDS (Ingall 2003) and MAST-I trials (Wardlaw 1999a) suggested that the risk reduction for death or dependency varied with stroke severity, being largest for participants with moderate stroke (NIHSS score around 10 to 15) and least in severe stroke (NINDS score around 18 to 30). However, these findings were based on small numbers in post-hoc analysis and need to be verified prospectively in larger randomised trials. A first attempt has now been made in the IST3 2012 trial. In IST-3 severity was well balanced between the study arms through minimisation and more than 30% of all participants had a NINDS score of 15 or more, Furthermore, case fatality was 20% or more in the control group. The participants with more severe stroke had at least the same benefit of thrombolytic treatment as those with less severe stroke.

Effect of time to treatment (randomisation): death or dependency at the end of follow-up

There was a significant reduction in the number of dead or dependent participants allocated thrombolysis who were randomised within three hours (57.4% of those allocated to thrombolysis were dead or dependent compared with 67% of those allocated to control, OR 0.66, 95% CI 0.56 to 0.79, P = 0.00001; 10 trials, 2160 participants) with no statistically significant heterogeneity (P = 0.91) (Analysis 1.16). In absolute terms, this is equivalent to 95 (95% CI 55 to 136) fewer dead or dependent participants per 1000 treated with thrombolysis (all drugs combined). In trials testing rt-PA, 59.3% of those allocated rt-PA were dead or dependent compared with 68.3% % of those allocated to control, OR 0.65 (95% CI 0.54 to 0.80, P < 0.0001; 6 trials, 1779 participants) with no significant heterogeneity, equivalent to 90 per 1000 fewer (95% CI 46 to 135) dead or dependent participants with rt-PA. Thus, heterogeneity present in the analysis of all trials, all time windows and drugs, is removed for participants randomised within three hours of stroke. This reinforces the previous finding of no heterogeneity for rt-PA and is presumably due to the fact that the vast majority of the participants (82.4%) in this analysis were treated with rt-PA, an effect of the inclusion of the IST3 2012 trial.

To compare these data on the effects of treatment given within three hours with the effects when given after three hours, we examined only those trials that reported data for both time windows (ASK 1996; ATLANTIS A 2000; ATLANTIS B 1999; Chen 2000; ECASS 1995; ECASS II 1998; IST3 2012; MAST-E 1996; MAST-I 1995) to avoid confounding by other differences between trials (Analysis 1.17; 9 trials, 6941 participants). Although there appeared to be more reduction in death or dependency in participants treated within three hours, the difference was not significant: three hours, OR 0.69, 95% CI 0.55 to 0.85; between three and six hours OR 0.99, 95% CI 0.88 to 1.10, (I^2 = 28%, P = 0.13).

In trials using rt-PA alone, amongst trials randomising in both less than three-hour and three- to six-hour time windows, the effect of treatment was not significantly different when given within three hours (OR 0.68, 95% CI 0.53 to 0.87; 5 trials, 1155 participants), or more than three hours after stroke (OR 0.97, 95% CI 0.85 to 1.09; 5 trials, 1449 participants), (I^2 = 45%, P = 0.06) (Analysis 1.18). Comparing all rt-PA trials whether they randomised only under three hours or only between three and six hours or from zero to six hours made little difference (Analysis 1.19): within three hours OR 0.65, 95% CI 0.54 to 0.80; 6 trials, 1779 participants; between three and six hours OR 0.93, 95% CI 0.83 to 1.04; 7 trials, 4950 participants. This should not be interpreted to mean that time to treatment is unimportant, but rather that other factor(s) like stroke severity may have confounded the association between time and outcome, and cannot be corrected for in this tabular analysis.

We also compared the outcome death or dependency at the end of follow-up across all trials stratified by their latest time allowed to randomisation (Analysis 1.20). This provided data at up to three hours, up to 4.5 hours, up to six hours, up to nine hours and up to 24 hours. There was surprisingly little difference in ORs for each time point: zero to three hours, OR 0.62, 95% CI 0.45 to 0.85 (1 trial, 624 participants); zero to 4.5 hours, OR 0.93, 95% CI 0.66 to 1.32 (2 trials, 1161 participants); zero to six hours, OR 0.81, 95% CI 0.69 to 0.95 (15 trials, 6883 participants); zero to nine hours, OR 0.74, 95% CI 0.35 to 1.59 (3 trials, 325 participants); zero to 24 hours OR 0.14, 95% CI 0.01 to 1.76 (1 trial, 16 participants); I^2 = 35%, P = 0.05.

An analysis of the effect of time on the proportion of participants who were alive and independent (Analysis 1.21; 8 trials, 6750 participants) or alive and with favourable outcome (Analysis 1.22; 6 trials, 1779 participants) for trials testing rt-PA (other trials not assessed) suggested that earlier treatment increased the proportion with better outcomes than later treatment: for every 1000 participants given rt-PA within three hours, 90 more would be alive and independent (P < 0.0001) with no heterogeneity,

compared with 10 more if treated between three and six hours after stroke (P = 0.58).

Effect of time to treatment (randomisation): death during follow-up

Data on participants treated within three hours of stroke are available for 11 trials (Analysis 1.23). The NINDS 1995 trial contributes 29% of the data on all drugs (624/2187 participants). There was no excess of deaths during follow-up with thrombolysis: 25.5 % of participants allocated to thrombolysis versus 25.8% of those allocated to control (OR 0.99 95% CI 0.82 to 1.21) but with statistically significant heterogeneity (I^2 = 65%, P = 0.0008). The main outlier was the MAST-I 1995 streptokinase-plus-aspirin-allocated participants who showed a significant excess of deaths even with treatment within three hours. In trials using rt-PA, the equivalent figures were OR 0.91 (95% CI 0.73 to 1.13, P = 0.39; 7 trials, 1806 participants), with no statistically significant heterogeneity (P = 0.22) and 14 fewer per 1000 deaths (95% CI 26 fewer to 55 fewer).

To compare treatment within three hours with treatment between three and six hours, we performed a similar analysis to those above for death and dependency (Analysis 1.24). Here there was a significant difference in treatment effect between those treated within three hours (OR 1.08, 95% CI 0.86 to 1.35; 9 trials, 1536 participants) and between three and six hours (OR 1.29, 95% CI 1.13 to 1.48; 9 trials, 5400 participants) after the stroke (I^2 = 63%, P = 0.0002) for all trials providing data in both time windows. For just trials testing intravenous rt-PA (Analysis 1.25), there was a marginally significant excess of deaths for participants treated between three and six hours (OR 1.17, 95% CI 1.00 to 1.38; 5 trials, 4044 participants), compared with those treated within three hours (OR 0.97, 95% CI 0.75 to 1.26; 5 trials, 1155 participants. I^2 = 46%, P = 0.05). Including all rt-PA data (i.e. all trials, all time windows) (Analysis 1.26) made little difference: within three hours: OR 0.91, 95% CI 0.73 to 1.13; 7 trials, 1806 participants; between three and six hours OR 1.16, 95% CI 1.00 to 1.35 (P = 0.07); 7 trials, 4966 participants.

We also compared the outcome death at the end of follow-up across all trials stratified by latest time to randomisation (Analysis 1.27). This provided data at up to three hours, up to 4.5 hours, up to six hours, up to nine hours and up to 24 hours. Although 'wobbly', there appeared to be an increase in ORs with increasing latest time to randomisation (and this was also just statistically significant, P = 0.04), but bear in mind that there are other major differences between these studies and very few data for later time windows: zero to three hours, OR 0.79 (95% CI 0.53 to 1.17; 2 trials, 651 participants); zero to 4.5 hours, OR 1.43 (95% CI 1.01 to 2.03; 2 trials, 1161 participants); zero to six hours, OR 1.12 (95% CI 0.99 to 1.26; 16 trials, 6886 participants); zero to nine hours, OR 2.10 (95% CI 0.79 to 5.58; 3 trials, 325 participants); zero to 24 hours, OR 1.00 (95% CI 0.14 to 7.10; 1 trial, 16 participants; I^2 = 33%, P = 0.07).

Effect of time to treatment (randomisation) - symptomatic intracranial haemorrhage (SICH)

Data are available on SICH from trials randomising both in under three hours and between three- and six-hour time windows for five rt-PA trials (ATLANTIS B 1999; ATLANTIS A 2000; ECASS 1995; ECASS II 1998; IST3 2012) (Analysis 1.28). Within three hours, there was an excess of SICH with rt-PA (OR 4.25, 95% CI 2.53 to 7.16; 1155 participants). This did not differ to the increase in SICH in participants randomised between three and six hours (OR 3.62 , 95% CI 2.76 to 4.76; 4013 participants; I^2 = 0%). When data from all rt-PA trials were included (that is, those randomising only within three or only between three and six hours) (Analysis 1.29), there was little difference: within three hours OR 4.55 (95% CI 2.92 to 7.09; 6 trials, 1779 participants); between three and six hours OR 3.73 (95% CI 2.86 to 4.86; 7 trials, 4935 participants; I^2 = 0%).

We also compared the outcome SICH across all trials stratified by latest time to randomisation (Analysis 1.30). There was surprisingly little difference in ORs for each time point: zero to three hours, OR 5.85 (95% CI 1.54 to 22.26; 2 trials, 651 participants); zero to 4.5 hours, OR 6.56 (95% CI 2.51 to 17.18; 2 trials, 1161 participants); zero to six hours, OR 4.20 (95% CI 3.21 to 5.50; 15 trials, 6951 participants); zero to nine hours, OR 6.82 (95% CI 0.88 to 52.78; 3 trials, 325 participants); zero to 24 hours, no SICH in AUST 2005; I^2 = 23, P = 0.17.

Effect of age under or over 80 years on death or dependency and alive and independent

We analysed the effect of age in just the rt-PA trials. Three trials included participants aged over 80 years (EPITHET 2008; IST3 2012; NINDS 1995), most coming from IST3 2012. With treatment up to six hours, the effect of rtPA on reducing the proportion of participants who were dead or dependent aged over 80 years (OR 0.80, 95% CI 0.64 to 0.99, P = 0.04; 3 trials, 1696 participants) was the same as in participants aged up to and including 80 years (OR 0.85, 95% CI 0.76 to 0.95, P = 0.004; 10 trials, 5175 participants) (Analysis 1.31). For participants treated within three hours (Analysis 1.32), those aged over 80 (OR 0.56, 95% CI 0.40 to 0.78, P = 0.0007; 2 trials, 726 participants) did as well as those aged up to or including 80 years (0.66, 95% CI 0.52, 0.85, P = 0.001; 6 trials, 1039 participants) with no heterogeneity. There was similarly little difference between the proportions of those aged under or over 80 years who were alive and independent after rt-PA whether treated up to six hours (Analysis 1.33; 10 trials, 6885 participants), within three hours (Analysis 1.34; 6 trials, 1779 participants) or between three and six hours (Analysis 1.35; 7 trials, 4971 participants).

Selection using CT scanning or Magnetic Resonance diffusion and perfusion (DWI/PWI) mismatch

We restricted this analysis to just trials testing intravenous thrombolysis. Eleven trials contributed data on selection using CT scanning (ATLANTIS A 2000; ATLANTIS B 1999; Chen 2000; ECASS 1995; ECASS II 1998; ECASS 3 2008; IST3 2012; MAST-E 1996; MAST-I 1995; NINDS 1995; Wang 2003) and four trials contributed data on selection using DWI/PWI mismatch (DEDAS 2006; DIAS 2005; DIAS 2 2008; EPITHET 2008). We included the EPITHET trial in the DWI/PWI section, although participants were not actually selected for inclusion on the basis of the MR findings, but rather on the basis of plain CT. However EPITHET obtained MR DWI/PWI data prior to randomisation and provided data on mismatch findings in relation to thrombolysis effect. Amongst 8334 participants selected on the basis of plain CT, 19% allocated thrombolysis and 19.3% allocated control were dead at the end of follow-up (OR 1.12, 95% CI 1.00 to 1.25; 15 trials); amongst 426 participants selected on the basis of DWI/PWI mismatch, 14% allocated thrombolysis and 8.2% allocated control were dead at the end of follow-up (OR 2.05, 95% CI 1.02 to 4.15; 4 trials) (Analysis 1.36). Amongst 7843 participants selected on the basis of plain CT, 60.5% allocated thrombolysis and 66.3% allocated control were dead or dependent at the end

of follow-up (OR 0.81, 95% CI 0.73 to 0.89; 11 trials); amongst 425 participants selected on the basis of DWI/PWI mismatch, 58.6% allocated thrombolysis and 61.2% allocated control were dead or dependent at the end of follow-up (OR 0.88, 95% CI 0.58 to 1.35; 4 trials) (Analysis 1.37). Amongst 8358 participants selected on the basis of plain CT, 8.1% allocated thrombolysis and 1.9% allocated control developed SICH (OR 4.38, 95% CI 3.38 to 5.69; 16 trials); amongst 426 participants selected on the basis of DWI/PWI mismatch, 6.4% allocated thrombolysis and 0% allocated control developed SICH (OR 7.51, 95% CI 1.40 to 40.35; 4 trials) (Analysis 1.38). These differences between selection by CT and by DWI/PWI mismatch were not statistically different.

Four studies (ECASS II 1998; IST3 2012; NINDS 1995; PROACT 2 1999) assessed ischaemic tissue extent on plain CT according to the ASPECT score, 8 to 10 versus 0 to 7, and the probability of being alive and independent (mRS 0 to 1) by end of follow-up after thrombolysis (Analysis 1.39). In all, 4567 participants provided data for this analysis. Among the 3317 participants with an ASPECT score indicating no or only a small area of ischaemic change (ASPECT 8 to 10), 38.9% of those allocated control versus 43.4% of those allocated thrombolysis had a favourable outcome (mRS 0 to 1) at the end of follow-up, (OR 1.21, 95% CI 1.06 to 1.39, P = 0.006; 4 trials, I^2 = 79%, P = 0.002). For the 1250 participants with an ASPECT score indicative of more extensive ischaemia (ASPECT 0 to 7) 19.3% of participants allocated control versus 22.5% of participants allocated thrombolysis were alive and independent (OR 1.20, 95% CI 0.91 to 1.58, P = 0.19; 4 trials), with no heterogeneity (I^2 = 1%, P = 0.39). However, there was heterogeneity between the effect of rt-PA in the participants with no or mild and extensive ischaemic change on CT (I^2 = 60, P = 0.01). In this relatively small sample tested for the effect on outcome by grade of CT-visible infarction, there were several types of drugs and different administration (pro-urokinase intra-arterially and rt-PA intravenously) which may account for the between-group heterogeneity.

Trials testing intra-arterial thrombolysis

Amongst participants allocated to thrombolysis, 56.6% were dead or dependent at the end of follow-up compared with 70.3% of those allocated to control, OR 0.49 (95% CI 0.31 to 0.79; 4 trials, 350 participants) (Analysis 1.40). This can be compared crudely with analysis of death or dependency for the combined intravenous thrombolysis trials which gave an OR of 0.79 (95% CI 0.71 to 0.89). These are not direct comparisons, and there are many other differences between the trials apart from the route of administration; this analysis should therefore be regarded with extreme caution. A separate Cochrane review presents the evidence, at present very limited, on direct randomised comparisons of intravenous with intra-arterial thrombolysis (Wardlaw 2013).

DISCUSSION

Summary of main results

There is strong evidence from 27 trials in 10,187 participants on the immediate hazards and the apparent net benefit of thrombolytic therapy given up to within three hours of acute ischaemic stroke, with overall benefit suggested up to six hours, for people aged over or under 80 years, and with different stroke severities. Overall, thrombolytic therapy was associated with a significant excess of deaths within the first seven to 10 days, symptomatic and fatal intracranial haemorrhages and (for all drugs) deaths by the end of follow-up. Most of the excess of deaths with thrombolysis occurred early and was explained by fatal intracranial haemorrhage. However, dependency was reduced in survivors so overall there was a significant net benefit. For every 1000 people treated with thrombolysis, 41 avoided death or dependency. Treatment within three hours resulted in 95/1000 fewer dead or dependent people. Trials using intravenous recombinant tissue plasminogen activator (rt-PA) contributed the most data to this review, and rt-PA appeared more favourable. Nevertheless, it was associated with an excess of early deaths, virtually all attributable to fatal intracranial haemorrhage (ICH), and a significant excess of symptomatic intracranial haemorrhage (SICH), but a neutral effect on deaths by the end of follow-up, and significantly more people avoiding dependent survival. If the factors associated with early fatal ICH can be identified (Whiteley 2012), then it may become easier to identify those who are at greatest risk of harm and clarify the risk-to-benefit ratio for thrombolysis. There was no clear increase in hazard (ICH or death) with increasing time up to six hours after stroke, although there was some evidence of decreasing benefit (reduction in death and dependency). Therefore, increasing time to treatment may reduce benefit more than it increases the hazard of thrombolysis.

IST3 2012 has provided substantial new data since the last update, and includes a wide range of participants that has helped to answer questions about how to select patients (to maximise benefit and minimise hazard), by using the variables age, time from onset, stroke severity, stroke subtype, role of imaging findings and co-morbidities. However, questions remain about whether hazard can be minimised by novel thrombolytic drugs, different doses and routes or speed of administration (Wardlaw 2013) or strategies to improve access of rt-PA to the occluding thrombus (e.g. ultrasound or glyceryl trinitrate (GTN)): some trials addressing these questions are ongoing or are in the planning stages.

There is now good data on the effect of thrombolytic therapy in the elderly, in whom stroke is most common. Prior to IST3 2012, only EPITHET 2008, MAST-E 1996, MAST-I 1995, and NINDS 1995 did not have an upper age limit but they included few participants (69 in NINDS and 25 in EPITHET) older than 80 years. People over 80 constitute a significant and increasing proportion of patients with stroke. The European license has an upper age limit of 80 years and has further strict selection criteria compared with the USA, where the license is based mainly on the NINDS 1995 trial and does not have an upper age limit. Among other limitations in Europe, an upper limit of stroke severity has also been introduced, as has a contraindication in people with the combined occurrence of diabetes and previous stroke. Hopefully these new data showing similar benefits of rt-PA in older as in younger people, particularly if treated within three hours of stroke, will lead to a relaxation of the licence.

Despite the large increase in available data with the inclusion of IST3 2012 (and near doubling of data for rt-PA) there is still significant between-trial heterogeneity for death or dependency at the end of follow-up both for trials testing rt-PA, and for all thrombolysis trials together. For rt-PA, there is heterogeneity for death or dependency whether defined as modified Rankin Score (mRS) 3 to 6 or 2 to 6. This indicates that more data are needed to provide more robust results. The need for more data from new trials is also supported by the fact that the data are relatively unstable.

For example, changing the definition of death or dependency from mRS 3 to 6 to 2 to 6 increases the heterogeneity for all thrombolysis trials (and is still present for just rt-PA trials) (Wardlaw 2000). In this latter analysis, although the overall conclusion of the trials combined was not materially altered, some individual trials 'wobbled' between being statistically significantly positive to statistically non-significant on moving from Rankin score 2 to 6 to 3 to 6, and vice versa (ECASS II 1998; ECASS 3 2008; PROACT 2 1999; Wardlaw 2000), with the most recent victim of this play of chance being IST3 2012. The fact that a neutral trial can become positive, or vice versa, or heterogeneity can be apparently removed by such a small alteration in the endpoint analysed simply emphasises the instability of the data and also advocates for alternative more robust ways of analysing data. The heterogeneity could have arisen from many sources, including differences in the design of the trials, in the type of participants included, in the availability of data to contribute to the present analysis (not all trials contributed data to all outcome analyses), and in the fact that these can only be considered as small trials for a condition as heterogeneous as ischaemic stroke. Individual data will be able to examine whether factors such as sex, blood glucose, etc. influence the effect of thrombolysis (Kent 2005a; Kent 2005b; Kent 2007; Mann 2005; Sandercock 2006). Comparisons of different thrombolysis drugs, doses and routes of administration are addressed in a separate Cochrane review (Wardlaw 2013).

There was a suggestion that the presence of a visible recent infarct on the CT scan prior to randomisation may be related to increased hazard (risk of ICH and death) but this was based on a post-hoc analysis of the CT scans in ECASS 1995, in which the baseline CT scans were not read blind to follow-up CT scans. Some trials had CT-visible infarction exclusion criteria and some, including NINDS 1995, did not. The reported rate of CT-visible infarction varied between trials, either reflecting differences in participant selection, observer sensitivity, or definition of visible infarction signs. We have now been able to include data on CT-visible infarct extent categorised using the ASPECTS score from secondary analyses of CT scans in several trials. We did not find any evidence of an interaction between visible infarct extent and rt-PA on death or dependency. Other possible risk factors identifiable on the CT scan that might interact with rt-PA (such as evidence of small vessel disease), are being addressed in IST3 2012. Whether or not other, more advanced imaging modalities, such as CT perfusion or magnetic resonance (MR) diffusion with perfusion, would improve patient selection or allow an extension of time window to treatment is the subject of ongoing trials (EXTEND). At present, the modest data available in an indirect comparison do not suggest that selection on the basis of MR diffusion- or perfusion-weighted imaging (DWI/PWI) leads to better effect of thrombolysis than for those selected on the basis of plain CT (Analysis 1.36; Analysis 1.37).

Overall completeness and applicability of evidence

The trials included in this review are small in comparison with the thrombolytic therapy in myocardial infarction trials. Nonetheless, this version of the review, with the addition of IST3 2012, includes a wider range of participants, with many more aged over 80 years, than previous versions. This is an effect of the principal methodology of IST3 2012 with the application of the uncertainty principle, which states that when there is a clear indication for treatment the person should be treated, and when there clearly is a contraindicated the person should not be treated; only where the tested treatment is promising but unproven could the participant be randomised. This approach provides the chance to test wider treatment criteria. There are substantially more data with the inclusion of 3035 participants from IST3 2012. However, not all trials contributed to all analyses, some analyses only include five or so trials and there were imbalances in stroke severity and age between treatment groups in some earlier trials. There remains significant heterogeneity for some outcomes and lack of a complete picture of the sources of heterogeneity, meaning that there is scope for more trials. This is particularly the case for mild strokes. Although there is a lack of information on concomitant aspirin usage, it seems fairly clear from MAST-I 1995 and the non-random comparisons in Analysis 1.14 that aspirin (or other antithrombotic drugs) given at the same time as thrombolysis is hazardous. The adverse effect of aspirin together with rt-PA was confirmed in one recent trial that stopped prematurely due to excess bleeding with aspirin and rt-PA combined (Zinkstok 2008). We have not been able to identify clear reasons why some people do poorly with thrombolysis. For example, the absence of any apparent time dependence of SICH with thrombolysis suggests that some other non-time-dependent factors may increase haemorrhage risk - i.e., not the presence of acute ischaemic change or other time-dependent factors. In contrast, the benefit of thrombolysis declines with time, fewer patients being alive and independent the later the treatment. The independent data meta-analysis of all rt-PA trials may be better able to identify factors influencing hazard.

The time window beyond which there is unlikely to be any benefit (or too much hazard) with thrombolytic therapy is unclear. The modifiers of the adverse effects of thrombolytic mode of action remain undetermined. There is a clear time dependency, with fewer participants treated within three hours of stroke being dead or dependent, than participants treated between three and six hours, but the latest time window remains undetermined. Other trials that tested other thrombolytic regimens beyond six hours suggest that the benefit may extend to nine hours or even longer in selected people. Although these trials were themselves not positive, when combined the overall result suggests that thrombolysis reduces death or dependency even at these later times. Thus, the time window for benefit probably extends to, and even beyond, six hours in selected people. However, this should not encourage complacency about the need for speedy treatment in ischaemic stroke. It simply underlines the need for more data so as to be able to provide individually-tailored treatment accounting for age, sex, stroke severity, prior aspirin use, brain scan appearances, etc., to name but a few factors in addition to time, which are likely to affect thrombolysis effect.

There is little information on which thrombolytic drug might have most benefit and least hazard, and there is little information on which dosage of drug has least hazard and most benefit (Wardlaw 2013). Direct randomised comparisons would be required (Dundar 2003). The Chinese UK trial (Chen 2000) had two doses of urokinase, but was underpowered to detect any difference between them. Similarly, the DEDAS 2006, DIAS 2005, and DIAS 2 2008 trials were together underpowered to detect a difference between doses of desmoteplase. Note that further details on direct randomised comparisons of drug or dose are included in a separate Cochrane Review (Wardlaw 2013), for which there are few additional data since its original publication.

There is limited information about the effect of thrombolysis on survival in a longer time frame, as most of the trials (all of the recent rt-PA trials) performed the follow-up at three months. NINDS 1995 published data on functional outcome at six months and one year which indicate that the effect of rt-PA was sustained beyond three months. IST3 2012 published data on functional outcome and death at 18 months which also indicate long-term benefits, but there are few other data on whether the benefit of thrombolysis is sustained (or even increases) at one year. This information is important for understanding the impact of thrombolytic treatment on health economics.

It is difficult to assess the cost effectiveness of thrombolytic treatment. A review for the UK National Health Service Health Technology Assessment (HTA) Programme on the cost effectiveness of thrombolytic treatment for acute ischaemic stroke needs to be updated (Sandercock 2002). One trial has a prospective substudy ongoing for the measured and modelled evaluation of cost effectiveness (IST3 2012).

Quality of the evidence

The overall quality of evidence, particularly for the drug with the majority of data, rt-PA, is good. The concerns about quality in earlier trials are largely overcome. The recent trials had good allocation concealment, central telephone randomisation, central blinded follow-up, and very few losses to follow-up.

Potential biases in the review process

This review is the result of an ongoing process involving the collaborative effort of many researchers worldwide and the principal investigators of many of the thrombolysis trials. At present, this review represents all of the evidence from the randomised controlled studies on the effects of thrombolytic therapy on acute ischaemic stroke. Comparisons of trials using different thrombolytic drugs should be treated with caution as these comparisons are indirect; available data on direct comparisons are presented in the companion review (Wardlaw 2013). We have tried to include all available tabular data and have checked the accuracy of it rigorously. We have tried not to miss any relevant completed trials. We can only apologise if we have overlooked some available data on an outcome in an included trial or have overlooked a trial completely.

Agreements and disagreements with other studies or reviews

A more detailed individual patient data meta-analysis of the streptokinase trials, using data from MAST-E 1996, MAST-I 1995 and ASK 1996, has been completed (TAS-PP 1999); urokinase trials (Jin Urokinase metaanalysis 2000) have been completed, and three rounds of a meta-analysis of individual data from the rt-PA trials have been published (rt-PA pooled analysis 2004; rt-PA pooled analysis 2008; TTAS) with a third completed and accepted for publication (in press). The analyses based on tabular data in the present review are consistent with these individual patient data analyses.

The SICH, death and functional outcome rates in the large registry of people treated open-label with rt-PA (SITS-MOST) are also similar to those found in the randomised trials. However, patient surveys are ultimately voluntary and therefore are inevitably prone to potential bias through incomplete data.

AUTHORS' CONCLUSIONS

Implications for practice

1. Taken overall, in people given thrombolysis in the acute phase of ischaemic stroke, there appears to be a net benefit of a significant reduction in the proportion who are dead or dependent at the end of follow-up across all drugs and time windows.
2. Faster treatment is more beneficial. People treated within three hours of stroke are less likely to be dead or dependent than those treated after three hours, although some may still derive benefit if treated up to six hours.
3. There is, overall, proof of an excess risk of symptomatic and fatal intracranial haemorrhage and early death from all causes with thrombolytic therapy. Evidence on risk factors, however, is incomplete.
4. More data are available for recombinant tissue plasminogen activator (rt-PA) than for other drugs; with rt-PA, there was no net effect on death from all causes at long-term follow-up.
5. People aged over 80 derive as much benefit from rt-PA as do those aged under 80 years, especially if treated within three hours of stroke.
6. Despite the overall net benefit, the available data do not provide sufficient evidence to determine the duration of the therapeutic time window, the clinical or radiological features which identify those most likely to benefit (or be harmed) including whether or not people with mild stroke benefit or not, or the optimum agent (or dose or route of administration).
7. The data indicate that antithrombotic treatment should be avoided until at least 24 hours after thrombolytic treatment.
8. In the light of these considerations, current evidence supports configuration of stroke services so as to be able to treat as many people as possible as fast as possible with the licensed drug rt-PA, including those aged over 80. There is no evidence to withhold rt-PA on the basis of age, early CT ischaemic changes, or severity of stroke if it can be administered within 4.5 hours and preferably within three hours. While the data suggest that some people may benefit even up to six hours, change in clinical practice should await results of further trials to determine the latest time window for benefit.

Implications for research

These data leave some uncertainties, which suggest that further large-scale randomised trials testing aspects of delivery of thrombolytic therapy in people with acute ischaemic stroke are needed:

1. To identify means of minimising the hazard without reducing the benefit, e.g. lower dose, avoiding people with specific characteristics (yet to be determined) or combinations of characteristics (e.g. elderly, severe stroke and some imaging feature), slower administration of the rt-PA bolus, different drug with lower haemorrhage risk, etc;
2. To provide data on the latest time window for treatment in which people and by what means of selection;
3. To provide data on benefits or harms of thrombolysis in mild stroke;
4. To provide randomised data on quality of life and cost effectiveness.

In future trials it would be helpful if data could be collected in such a way as to be compatible with the simple and fundamental effect parameters used in this review (e.g. early and late death, fatal intracranial haemorrhage, functional outcome). This would help to address the problem in the present review of between-trial heterogeneity (which may be exacerbated by missing data), and facilitate future meta-analyses.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abe 1981

Methods	Double-blind RCT Sealed drug prepacks Not intention-to-treat
Participants	All grades of presumed thrombotic stroke < 2 weeks, pre-entry CT, age 18 years and over Excluded: presumed embolic stroke, severe neurological deficit
Interventions	Tissue-cultured urokinase (Abbott Labs, USA) 60,000 U/day i.v. for 7 days versus identical-looking placebo
Outcomes	Global Improvement Rating and safety assessment at 4 weeks after treatment start (including follow-up CT if neurologically deteriorated)
Notes	Further information from Prof Abe: 11 participants (6 treatment and 5 placebo) who received non-trial drugs outside the trial protocol were excluded from analysis prior to breaking the randomisation code plus 2 who underwent superficial temporal artery-middle cerebral artery bypass surgery Published in Japanese

ASK 1996

Methods	Double-blind, central telephone randomisation RCT Sealed drug prepacks of streptokinase or identical-looking placebo Intention-to-treat
Participants	Any acute ischaemic stroke (though not very mild or rapidly recovering) that could be randomised and treatment start within 4 hours of clearly defined symptom onset; age > 18 years and < 85 years; CT scan mandatory to exclude cerebral haemorrhage pre-randomisation Excluded: people with recent trauma or surgery, stroke within the last 3 months or at any time if in the same hemisphere as the presenting stroke, pregnancy, any anticoagulants given within the previous 48 hours (except aspirin), uncontrolled hypertension (systolic BP > 200 mmHg, diastolic > 120 mmHg)
Interventions	Streptokinase (Hoechst, Australia) 1.5 MU in 100 ml of normal saline i.v. over 1 hour versus identical-looking placebo (prepared by Berhingwerke, Germany, in association with Hoechst) Infusion to be stopped and i.v. Haemaccel given (plasma expander) should the BP fall below 100 mmHg systolic (or by more than 20 mmHg from the initial systolic BP) during the infusion This procedure to be repeated should hypotension occur again, but the infusion to be completed within 3 hours or abandoned Aspirin 100 mg to be given orally within 4 hours of the trial treatment infusion and thereafter daily for the duration of the study No other anticoagulants to be given within 48 hours of the trial treatment
Outcomes	Death and dependency at 3 months assessed by the Barthel Index, i.e. favourable outcome = alive and Barthel Score > 60, unfavourable = dead or Barthel Score < 60

ASK 1996 *(Continued)*

	CT scan at 7 to 10 days (or sooner if clinically indicated) to look for cerebral haemorrhage
Notes	Terminated prematurely after randomisation of 340 (of the intended 600) participants, initially just the 3 to 4 hour randomisation (because of significant excess early mortality in the streptokinase group) and then all randomisation because the randomisation rate within 3 hours was too slow to be viable Apparent excess of problems with hypotension during the streptokinase infusion compared with MAST-I 1995 and MAST-E 1996 (20% in ASK versus only a few % in the 2 MAST trials), and note routine use of aspirin within 4 hours of trial treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

Atarashi 1985

Methods	Double-blind RCT Sealed prepacked drug or placebo Not intention-to-treat
Participants	Presumed cerebral arterial thrombosis (angiography where possible) < 5 days, aged 18 years and up, entry CT Excluded: presumed embolic stroke, severe neurological deficit
Interventions	High-dose UK (240,000 u/day i.v. for 7 days) versus low dose (60,000 u/day i.v. for 7 days) versus identical-looking placebo The high- and low-dose participants were analysed as 1 group for the purpose of this review, i.e. the comparison is 'any UK treatment versus placebo'
Outcomes	Clinical improvement (Final Global Improvement Rating) at 4 weeks from start of treatment, safety (absence of side effects), including follow-up CT if neurological deterioration
Notes	Further information provided by Prof Ohtomo, co-investigator 6 participants (4 treated low-dose, 2 placebo) were excluded from analysis prior to breaking the randomisation code as the diagnosis thought not to be stroke

ATLANTIS A 2000

Methods	Double-blind, placebo-controlled RCT; August 1991 to November 1993 Randomisation was by selection of a numbered treatment pack held in the participating centre (of tPA or identical-looking placebo); the numbered pack had been identified by telephoning the trial co-ordinating centre in advance of the arrival of the next participant to be randomised Once administered, the trial co-ordinating centre was telephoned to inform them of the participant's details and identify the next treatment pack to be given to the next participant to be randomised
Participants	Any acute ischaemic stroke that could be randomised and start treatment within 6 hours of clearly-defined stroke onset Participant selection criteria believed to be otherwise similar to those in the NINDS 1995 trial CT scan mandatory prior to randomisation to exclude cerebral haemorrhage, but no exclusion criteria based on visible infarction Age: 18 - 80 years

ATLANTIS A 2000 *(Continued)*

Interventions	Alteplase (tPA - Activase, Genentech, South San Francisco) 0.9 mg/kg body weight to a maximum of 90 mg, in 100 ml normal saline, the initial 10% given as a bolus and the rest over an hour i.v. Blood pressure control as for NINDS 1995 Aspirin and anticoagulants to be avoided for the first 24 hours, but could be used thereafter
Outcomes	NIH Stroke Scale improvement at 30 days Death and dependency at 90 days (modified Rankin 2 to 6) Barthel NIH Stroke Scale Cerebral haemorrhage on repeat CT The final follow-up assessment was performed by a neurologist who had not cared for the participant at randomisation or during the first few days after treatment
Notes	Stopped in November 1993, protocol modified and continued as ATLANTIS B 1999 in the same centres 42 active centres, 142 participants randomised

ATLANTIS B 1999

Methods	Double-blind, placebo-controlled RCT Randomisation was by selection of a numbered treatment pack held in the participating centre (of tPA or identical-looking placebo); the numbered pack had been identified by telephoning the trial co-ordinating centre in advance of the arrival of the next participant to be randomised Once administered, the trial co-ordinating centre was telephoned to inform them of the participant's details and identify the next treatment pack to be given to the next participant to be randomised
Participants	December 1993 to January 1996: 0 to 5-hour time window February 1996 to end of trial: 3 to 5-hour time window and CT exclusion criteria introduced (visible infarction in > ⅓ of the MCA territory excluded) Within the above time periods, anyone with acute ischaemic stroke with clearly defined symptom onset who could be treated within the specified time period Age 18 - 80 years CT pre-randomisation mandatory to exclude cerebral haemorrhage only until February 1996, but thereafter also to exclude visible infarction in more than ⅓ of the MCA territory 120 centres active
Interventions	Alteplase (tPA - Activase, Genentech, South San Francisco) 0.9 mg/kg to maximum dose of 90 mg in 100 ml normal saline or identical-looking placebo, the first 10% as a bolus and the rest infused over an hour i.v. Aspirin to be avoided within the first 24 hours, but could be used thereafter
Outcomes	NIHSS modified Rankin Scale (death or dependency = 2 to 6) BI at 90 days Death Cerebral haemorrhage (symptomatic and fatal) The final follow-up assessment was performed by a neurologist who had not cared for the participant at randomisation or during the first few days after treatment
Notes	Stopped in mid-1998 following a futility analysis, prior to the publication of ECASS II 1998 Data on all 619 participants randomised has not yet been presented, only on 547 randomised between 3 and 5 hours

AUST 2005

Methods	PROBE: Prospective Randomised Open controlled study with Blinded Endpoint assessment; RCT Location: multi-centre, 7 centres in Australia and New Zealand, ongoing January 1996 to May 2003 Method of randomisation: telephone to a central office (for 2 participants by coin tossing when system was unavailable, after consent from the Steering Committee) Analysis: intention-to-treat (LOCF)
Participants	Eligibility: people with clinical presentation of a posterior lesion and where CT and angiography supported an ischaemic stroke with a posterior circulation vascular occlusion and where the participant was judged suitable for long-term anticoagulation Age limits: 18 - 85 years NIHSS: not defined Time window: 0 to 24 hours Participants: - Treatment group: male: 7 (88%), mean age: 64.2 (± 11.1) years, mean delay (range): 710 (345 to 1305) minutes, NIHSS median (range): 23 (7 to 29), GCS: 6 (3 to 15) - Control group: male: three (38%), mean age: 63.7 (± 12.3) years, mean delay (range): 749 (205 to 1350) minutes, NIHSS median (range): 18 (5 to 29); GCS median (range): 12 (3 to 15) Baseline angiography findings available in 14 participants, 7 in treatment group, 7 in control group: basilar artery, unilateral vertebral artery/posterior inferior cerebellar artery, and unilateral PCA were included Number of randomised participants: 16 (8 in treatment group, 8 in control group)
Interventions	Treatment group: UK i.a. with increments of 100,000 IU to max 1,000,000 IU Control group: no thrombolysis All participants were anticoagulated acutely (5,000 IU heparin i.a. followed by i.v. heparin to a target APTT 60 to 80 for minimum 2 days, and then oral warfarin to a target INR of 1.5 to 2.5 for 6 months
Outcomes	Clinical at 6 months: mRS, BI, NIHSS assessed by a research nurse or neurologist blinded to treatment allocation and not involved in the participant's initial care, and determined by an independent outcomes committee blinded to all documentation at 6 months Primary efficacy endpoint was the combined morbidity (BI and mRS) and mortality at 6 months Pre-specified secondary endpoints were arterial re-canalisation at day 7 to 10 after treatment, neurological impairment at 6 months, safety and tolerability, and cost effectiveness
Notes	Study groups were unbalanced with more males and more severe strokes in the treatment group The trial was prematurely terminated in June 2003 due to slow recruitment, and withdrawal of sale of UK Given the small numbers of recruited participants only the primary endpoint and safety are presented

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

Chen 2000

Methods	Double-blind, placebo-controlled RCT Randomisation of a numbered treatment pack (UK or normal saline) held in the participating centre Blinded follow-up
Participants	People aged 35 to 75 years with clinical diagnosis of carotid distribution ischaemic stroke (including lacunar), within 6 hours of stroke No visible infarct on CT

Chen 2000 *(Continued)*

Interventions	UK (Roxin, Guangdong Techpool Biochem Pharma Co Ltd, China) Group A: 1.5 MU Group B: 1.0 MU Group C: placebo (normal saline) i.v. over 30 minutes
Outcomes	European Stroke Scale serially up to 90 days Barthel Index and modified Rankin Score at 90 days Assessment was by a doctor not involved in administering the trial drug
Notes	All participants also received low molecular weight dextran 500 ml i.v. per day for 10 days and 300 mg aspirin (starting 24 hours after thrombolysis) for 10 days

DEDAS 2006

Methods	Double-blind, randomised, placebo-controlled body-weight-adjusted dose-escalation study; RCT Location: 21 centres in the USA and 4 centres in Germany, between March 2003 and October 2004 Method of randomisation: interactive voice response system Analysis: intention-to-treat, analysis of target population defined before unblinding by the core laboratory to consist only of participants with mismatch and no isolated ICA occlusion In addition to the ITT analysis, a target population was defined before unblinding and included only those who had had mismatch and no isolated ICA occlusion (as determined by the core laboratory) MRI at screening, 4 to 8 hours post-treatment, and at 30 days CT was performed at 24 hours
Participants	Eligibility: principally according to NINDS 1995 criteria, but with NIHSS limits 4 to 20 and MRI evidence of DWI/PWI mismatch (20% mismatch with a perfusion deficit, with or without DWI lesion of > 2 cm in diameter and involving the cerebral cortex) Participants: age limits: 18 - 85 years NIHSS limits: 4 to 20 Time window: 3 to 9 hours Summary of participant characteristics: - Treatment groups: N = 37, male 55%, median age (range): 73 (42 to 85) years, NIHSS: 9 (4 to 19), time after onset to treatment: 449 (222 to 568) minutes, DWI lesion: 22.2 (1.6 to 78.1) ml - Control group: N = 8, male 63%, median age (range): 71.5 (42 to 85) years, NIHSS 12 (6 to 18), time after onset to treatment: 443 (220 to 516) minutes, DWI lesion volume: 35.1 (1.5 to 68.6) ml Number randomised: 37 (29 in the treatment groups; 8 in the control group)
Interventions	Desmoteplase i.v. administered as a bolus over 1 to 2 minutes 2 doses: 90 µg/kg (N = 14) and 125 µg/kg (N = 15) versus placebo (N = 8) Each dose tier included 15 treatment participants and 4 controls
Outcomes	Primary safety endpoint: rate of SICH as defined by CT and according to NINDS 1995 criteria Co-primary efficacy endpoint: reperfusion at 4 to 8 hours (≥ 30% reduction of MTT volume or ≥ 2 points improvement on MR-adjusted TIMI); clinical outcome at 90 days (good outcome composite of: NIHSS ≥ 8 points improvement or a score of 0 to 1, mRS 0 to 2, BI ≥ 75)
Notes	In 12 randomised participants the MRI-entry criteria had been violated: 6 had an isolated ICA occlusion; another 6 had either no mismatch or no perfusion deficit 6 of the violations occurred in the 90 µg/kg dose group, 4 in the 125 µg/kg group, and 2 in the placebo group The target population in total was 25 participants (placebo N = 6, 90 µg/kg N = 8, 125 µg/kg N =11)

Risk of bias

Bias	Authors' judgement	Support for judgement

DEDAS 2006 *(Continued)*

Allocation concealment (selection bias)	Low risk

DIAS 2 2008

Methods	Double-blind, randomised, controlled prospective single bolus study investigating the efficacy and safety of 2 doses versus placebo in participants with ≥ 20% mismatch as detected by MRI or perfusion CT Method of randomisation: interactive voice response system Imaging: MR (DWI/PWI) or CT perfusion Analysis: intention-to-treat
Participants	Eligibility: principally according to NINDS 1995 criteria, but with NIHSS limits 4 to 20 and MRI evidence of DWI/PWI mismatch with a distinct penumbra ≥ 20% on MRI or perfusion CT Age limits: 18 - 85 years NIHSS: 4 to 20 Time window: 3 to 9 hours Participants: - Treatment groups: 90 µg/kg bodyweight N = 57, 125 µg/kg bodyweight N = 66 - Control group: N = 63 Number randomised N =186 (treatment group N = 123, control group N = 63)
Interventions	Desmoteplase i.v. administered as a single bolus over 1 to 2 minutes; 2 doses: 90 µg/kg and 125 µg/kg versus placebo
Outcomes	Primary outcome included: clinical improvement day 90 defined by the composite endpoint: improvement in NIHSS ≥ 8 points or NIHSS 0 to 1, BI ≥ 75, and mRS 0 to 2 Primary safety endpoints: rate of SICH at 72 hours, and all-cause mortality
Notes	Trial information based on press release of June 2007 after report of the trial at the 16th European Stroke Conference, Glasgow 2007 There was increased mortality (14 deaths) in the 125 µg/kg bodyweight versus 90 µg/kg and placebo (among the 14 deaths, 10 were considered by the investigators to be unrelated to treatment, 9 were non-neurological, and 9 occurred more than 10 days after administration of the drug) Further information is sought The trial was halted on 25 October 2006 by the Data and Safety Committee (DCM) for apparent safety concerns which were not disclosed by the DCM; after 5 days the trial was allowed to resume enrolment without modification of the protocol and with remaining blinded data

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

DIAS 2005

Methods	Double-blind, randomised placebo-controlled, dose-finding, phase II trial Location: 44 centres in 12 countries, trial ongoing between January 2001and October 2003 Method of randomisation: interactive voice response system collected participant's date of birth, weight, and NIHSS score and participants were randomised to a dose of desmoteplase or placebo The trial was undertaken in 2 parts:

DIAS 2005 *(Continued)*

	- Part 1: 1st period: participants were allocated into 4 groups, 3 with fixed treatment doses, and 1 placebo-control group; 2nd period (from participant number 31): 1 fixed treatment dose versus placebo - Part 2: after participant 47, the trial continued as a dose escalation trial with 3 body weight-adjusted treatment doses versus placebo Stratification according to age: ≤ 75 years versus > 75 years Imaging inclusion method: MRI, DWI/PWI mismatch, perfusion abnormality > 2 cm in diameter involving hemispheric grey matter; DWI/PWI mismatch ≥ 20% MRI at screening, 4 to 8 hours post-treatment, and at 30 days CT was performed at 24 hours Analyses: included an intention-to-treat sample (deceased participants were given worst possible score for all outcomes; further missing data were analysed as LOCF observations); and per-protocol (104 randomised, 102 included in analyses)
Participants	Eligibility: people with ischaemic stroke and MRI evidence of mismatch involving hemispheric grey matter NIHSS limits for first 9 participants: 8 to 20, to increase recruitment widened limits from participant number 10: 4 to 20 and a prolonged time window from 3 to 6 to 3 to 9 hours After the first 5 participants a 30-minute MRI-to-treatment time requirement was applied Further, the upper limit of the DWI lesion at baseline was reduced from ⅔ to ⅓ of the MCA territory In addition, participants on any platelet inhibitor could be excluded at the discretion of the treating physician Patients: age limits 18 years - 85 years NIHSS: 4 to 20 Time window: 3 to 9 hours (first 9 participants: 3 to 6 hours, from participant number 10: 3 to 9 hours) Summary from both parts of trial: - Treatment groups: N = 75; male 55%, age (median) 68 years, NIHSS 12, time from onset 324 minutes, DWI lesion volume ml 17.76 - Control group: N = 27; male 52%, (median) age 68 years, NIHSS 12, time from onset 325 minutes, DWI lesion volume ml 20.40 Number randomised:104 (Part 1: 47, Part 2: 57) Of the 104 randomised participants, 2 control participants received no trial medication and were excluded from all analyses leaving for both parts 102 participants per protocol: treatment group 75; control group 27
Interventions	Desmoteplase i.v. administered as a bolus over 1 to 2 minutes Each dose tier included 15 treatment participants and 4 control participants Doses: - Part 1, 1st period: 25 mg, 37.5 mg, 50 mg versus placebo; 2nd period: 25 mg versus control - Part 2, dose titration from 62.5 µg/kg, 90 µg/kg to 125 µg/kg versus control Participants < 66 kg were administered 80% of the dose; participants ≥ 66 kg received 100%
Outcomes	Primary safety endpoint: SICH according to NINDS 1995 criteria, CT at 72 hours Primary clinical endpoint: combined NIHSS (0 to 1), mRS (0 to 2), and BI (≥ 8 points improvement or a score of ≥ 75) at 90 days Co-primary efficacy endpoints: reperfusion at 4 to 8 hours defined as ≥ 30% reduction of MTT volume or ≥ 2 points improvement on MRI-adapted TIMI grading Other endpoint: change in infarct volume on DWI from baseline to day 90
Notes	The trial with 3 doses versus control was discontinued by the Data Monitoring Committee (DMC) after the 30th participant and occurrence of 3 SICH in the 37.5 mg group and 1 in the 50 mg group After the 47th participant, excess SICH in the treatment group (25 mg) prompted a halt by the DMC, interim analysis, and subsequent amendment In Part 2 of the trial, a placebo-controlled bodyweight-adjusted dose-escalation design starting at a dose of 62.5 µg/kg, followed by 90 µg/kg and 125 µg/kg was applied Further, in association with the interim analysis of Part 1, the upper limit of blood sugar was reduced from 22 to 11 mmol/L (in Part 1 blood glucose > 10 mmol/L was associated with an increased risk of ICH)

DIAS 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

ECASS 1995

Methods	Double-blind RCT Sealed drug prepacks (no central telephone randomisation) Only intention-to-treat data used in this review
Participants	People with acute MCA territory ischaemic stroke who could be randomised and start treatment within 6 hours of symptom onset Pre-entry CT to exclude cerebral haemorrhage and people whose infarct was already visible; age > 18 years and < 80 years Excluded: people with mild strokes or whose symptoms were rapidly improving, in coma, BP > 110 diastolic and > 200 systolic; recent trauma or surgery, pregnancy, weight > 100 kg (because of dose limit)
Interventions	Actilyse (recombinant tissue Plasminogen Activator, tPA) 1.1 mg/kg body weight up to a maximum of 100 mg (Boehringer Ingelheim, Germany), or identical-looking placebo i.v. The first 10% of the total dose was given as a bolus followed by infusion of the remainder over 60 minutes All anticoagulants and aspirin to be avoided in the first 24 hours (subcutaneous heparin allowed); thereafter, the use of these drugs was at the discretion of the attending physician
Outcomes	Primary: BI and mRS scores at 90 days Secondary: case fatality at 30 days, various combined stroke scores at 90 days, duration of hospital stay Rankin 2 or worse = disabled on this modified scale: 0 = no symptoms, 6 = dead
Notes	Trial sponsored by Boehringer-Ingelhei Results presented as ITT analysis and 'Target Population', i.e. after exclusion of protocol violations most of which were due to visibility of early signs of cerebral infarction on the randomisation CT on review by the central CT monitoring committee In this review, only the ITT data have been used The published data were supplemented by additional information from the principal investigators, and with data presented at the meeting organised by the sponsors to present the results held in Barcelona in March 1995

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

ECASS 3 2008

Methods	Double-blind, randomised, placebo-controlled, parallel group efficacy and safety trial Location and time: 130 centres in 19 European countries, July 2003 to November 2007 Method of randomisation: interactive voice randomisation system

ECASS 3 2008 *(Continued)*

	Treatment packs of alteplase or matched placebo, in blocks of 4 at each centre and having been generated randomly centrally Investigators were blinded to the size of the blocks Blinded assessment at the time of enrolment at 1, 2 and 24 hours, and on days 7, 30 and 90 Analysis: intention-to-treat (worst possible outcome in cases who were known to be alive)
Participants	Eligibility: with the exception of the time window, the study drug was to be used in accordance with the current European licensing Age: 18 - 80 years NIHSS: 4 to 25 Time window: 3 to 4 hours (228 participants), and 3 to 4.5 hours (from participant 229 to 821) Imaging: CT or MR pre-randomisation to exclude ICH and major ischaemic infarction, repeated 22 to 36 hours after treatment Summary of participants enrolled: - Treatment group: age ± SD: 64.9 ± 12.2 years; male: 63%, NIHSS (mean): 10.7± 5.6; time from onset (median): 3 hours 59 minutes, 3 to ≤ 3.5 hours: 9.6%, 3.5 to ≤ 4 hours: 45.7%, 4 to ≤ 4.5 hours: 41.6% - Control group: age ± SD. 65.6 ± 11.0 years; male: 57%; NIHSS (mean): 11.6 ± 5.9; time from onset (median): 3 hours 58 minutes, 3 to ≤ 3.5 hours: 10.4%%, 3.5 to ≤ 4 hours: 47.9%, 4 to ≤ 4.5 hours: 36.7% Number randomised: total N = 821; treatment group N = 418 of which 375 received treatment; control group N = 403, of which 355 received placebo
Interventions	Actilyse (rt-PA) 0.9 mg/kg to a maximum dose of 90 mg (Boehringer Ingelheim, Germany) or identical-looking placebo with 10% given as an i.v. bolus and the remainder as a continuous infusion over 60 minutes
Outcomes	The primary efficacy endpoint: disability day 90 assessed by means of a dichotomised mRS (0 to 1) or unfavourable outcome (mRS 2 to 6) Secondary endpoint: composite global outcome: mRS 0 to 1, BI ≥ 95, NIHSS 0 to 1, and GCS = 1 Further functional endpoints: NIHSS improvement > 8, mRS 0 to 2 or 3 to 6, and BI ≥ 95 Safety endpoints: overall mortality at day 90, any ICH, SICH*, symptomatic brain oedema** * SICH = any apparent extravascular blood in the brain/within the cranium associated with a clinical deterioration > 4 on NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration To allow comparison with published data we also performed a post-hoc analysis of rates of SICH according to definitions used in other trials **Symptomatic oedema = brain oedema with a mass effect as predominant cause of clinical deterioration
Notes	Monitoring and data management by the manufacturer, Boehringer Ingelheim Subcutaneous heparin (< 10,000 IU) or equivalent doses of low molecular weight heparin was permitted ≤ 24 hours

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

ECASS II 1998

Methods	Double-blind, placebo-controlled RCT Randomisation by sequential numbered packs at each centre (the allocation having been generated randomly centrally)
Participants	Acute hemispheric ischaemic stroke, people aged 18 - 80 years, within 6 hours of onset, CT having excluded intracranial haemorrhage and visible infarction in more than ⅓ of the MCA territory

ECASS II 1998 *(Continued)*

Interventions	Actilyse (rt-PA) 0.9 mg/kg to a maximum dose of 90 mg (Boehringer Ingelheim, Germany), or identical-looking placebo, 10% given as a bolus and the rest infused over 1 hour, to be started within 6 hours of stroke onset Aspirin and anticoagulants (apart from subcutaneous heparin) to be avoided in the first 24 hours; thereafter the use of these drugs was at the discretion of the attending physician
Outcomes	Death or dependency at 90 days defined as modified Rankin 2 to 6 Intracranial haemorrhage Death Various other scores at 90 days
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

EPITHET 2008

Methods	Double-blind, randomised, prospective, phase II placebo-controlled study Location: 15 centres in Australia, New Zealand, Belgium and the UK during 2001 to 2007 Method of randomisation: computerised randomisation giving out the number of a treatment pack The packs were centrally prepared in blocks for each centre (4 treatment packs per block) Analysis: intention-to-treat, and of primary outcome measure: per-protocol
Participants	Acute hemispheric ischaemic stroke The participants were randomised on the basis of plain CT Age: ≥ 18 years NIHSS: ≥ 4; premorbid mRS ≤ 2 Time window: 3 to 6 hours Baseline CT (in one centre MRI) to exclude: haemorrhage and early ischaemic changes ≥ ⅓ of the MCA territory; CT was repeated in clinical deterioration possibly due to a haemorrhagic transformation MRI was performed before start of treatment, at day 3 to 5 (DWI, PWI/concentration-time curves after gadolinium, and MRA (time of flight or phase contrast)) At day 90 (T2-weighted images to measure final infarct volume) To standardise image analysis, all MRI were centrally read Number randomised: 101 (treatment group: 52; control group: 49)
Interventions	Alteplase (rt-PA) 0.9 mg/kg i.v. up to a maximum of 90 mg, 10% given as a bolus, the remainder as infusion over 1 hour, or placebo
Outcomes	MRI definitions and outcome measures: mismatch, PWI-DWI volume > 1 to 2, and PWI-DWI volume ≥ 10 ml; infarct growth, 4 measurements, i.e. expansion between baseline and day 90 T2-weighted lesion; reperfusion > 90% reduction between baseline and day 3 PWI volumes; recanalisation: improvement of TIMI from baseline to day 3 to 5 by ≥ 2 points; SICH according to SITS-MOST criteria; target mismatch, mismatch excluding 'malignant profile'; 'malignant profile': DWI volume ≥100 ml, PWI volume ≥ 100 ml, or both with PWI defined as T_{max} delay ≥ 8 seconds Clinical: NIHSS at day 3 to 5 and day 90; mRS day 90 Good neurological outcome: NIHSS 0 to 1 or improvement ≥ 8 from baseline Good functional outcome: mRS 0 to 2 Primary outcome measure: infarct growth Secondary outcome measures included: difference in mismatch participants in reperfusion; good neurological and functional outcome between the treatment and control group; difference in DWI le-

EPITHET 2008 *(Continued)*

	sion volumes in the treatment group between participants with and without SICH; difference in infarct growth in non-mismatch participants between the treatment arms; difference in infarct growth, good neurological and functional outcomes in the treatment group between participants with and without mismatch; difference in infarct growth, good neurological and functional outcomes in the treatment group between participants with target mismatch and those with 'malignant profile'
Notes	The paucity of participants without mismatch precluded comparisons of the effect of rt-PA in the presence versus absence of mismatch

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

Haley 1993

Methods	Double-blind, randomised, blinded, placebo-controlled RCT Sealed envelope treatment allocation, opened by pharmacist at randomisation and appropriate infusion made up Other study personnel remained blinded Not intention-to-treat
Participants	Ischaemic stroke < 90 or < 180 minutes from onset, 18 - 80 years, pre-entry CT Excluded: TIA, very mild and very severe neurological deficits
Interventions	Alteplase (tPA, Genentech) 0.85 mg/kg or identically appearing placebo i.v. over 60 minutes Early (0 to 90 minutes) versus late (91 to 180 minutes) treatment versus placebo, although in this review the early and late groups have been analysed together, i.e. the comparison is 'any tPA versus placebo'
Outcomes	Clinical improvement using NIH Stroke Scale at 24 hours, 2 + 7 days, and 3 months Follow-up CT at 24 hours, 7 days and 3 months for infarct volume and haemorrhagic transformation
Notes	Pilot for larger NINDS 1995 trial

IST3 2012

Methods	Randomised, open-label, controlled trial with blinded outcome assessments (PROBE)
Participants	Participants (n = 3035) with acute ischaemic stroke < 6 hours, no age limit Protocol at www.dcn.ed.ac.uk/IST3 or www.ist3.com
Interventions	I.v. rt-PA 0.9 mg/kg to maximum 90 mg versus placebo
Outcomes	Death at 7 days, SICH, death or dependency at 6 months
Notes	Moving from start-up to extended pilot phase in July 2002, trial ended 31 January 2012 and the main publication and a meta-analysis on rt-PA trials (11 earlier included plus IST-3) were both published in the *Lancet* 2012;379:2352-63 and 2012;379: 2364-72, respectively. The IST-3 trial protocol and the Statistical Analysis Plan had been published before the breaking of the code (all references available in reference list)

IST3 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised after core data entry was complete via the Internet or telephone, stratified by country and minimised on key prognostic variables
Allocation concealment (selection bias)	Low risk	Central web- or telephone-based randomisation ensured allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Treatment was given open-label, therefore participants and personnel knew whether rt-PA or control was used. However, all participants were to receive best medical care and there was no evidence of differences in care between treatment groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment was given open-label, therefore participants and personnel knew whether rt-PA or control was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Symptomatic and fatal ICH and all 6-month outcomes were adequately blinded to treatment. Haemorrhage was assessed centrally by scan adjudicators blind to all clinical details; 6-month outcomes were assessed centrally by staff blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very few data were lost to follow-up; no difference between trial groups
Selective reporting (reporting bias)	Low risk	All outcomes were reported; no difference in reporting between groups
Other bias	Low risk	No other biases evident

JTSG 1993

Methods	Double-blind RCT Sealed identical prepacks of drug or placebo Not intention-to-treat
Participants	Thromboembolic stroke < 6 hours, aged 18 - 80 years, pre-entry CT and angiography Excluded: haemorrhagic stroke or patent cerebral arteries at angiography
Interventions	Duteplase 20 MIU versus identical-looking placebo i.v. over 60 minutes Duteplase supplied by the Sumimoto Corporation, Japan
Outcomes	Reperfusion (immediate post-infusion angiography), clinical improvement using Hemispheric Stroke Scale (HSS) at 4 weeks after stroke, haemorrhagic transformation on follow-up CT, death
Notes	112 participants recruited, 14 excluded for protocol violations before breaking the randomisation code, analysis is of 98 patients who completed the study Further information provided by Prof Yamaguchi

Risk of bias

JTSG 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

MAST-E 1996

Methods	Double-blind, randomised controlled trial Central telephone randomisation Sealed prepacks of drug (streptokinase) or identical placebo Intention-to-treat
Participants	People with symptoms of large acute ischaemic stroke in the MCA territory who could be randomised and start treatment within 6 hours of symptom onset; age > 18 years but no upper limit; CT scan mandatory prior to randomisation to exclude cerebral haemorrhage Exclusions: people with mild neurological deficit (MAST Unified Scale > 55), or who were improving rapidly when assessed; previous disabling stroke; pregnancy; systolic BP > 220, diastolic BP > 110; oral anticoagulants (not aspirin); recent trauma, surgery, peptic ulcer disease, etc
Interventions	Streptokinase 1.5 MU in 100 ml normal saline i.v. over 1 hour versus identical-looking placebo Heparin and aspirin use were allowed in the first 24 hours (as well as later) at the discretion of the attending physician provided that the dose, route and time of administration were recorded
Outcomes	Death and disability (MAST unified scale, Rankin and Barthel scales) at 10 days and 6 months after randomisation (disability = Rankin 3 or worse); cerebral haemorrhage within the first 10 days; other adverse events (hypotension, systemic haemorrhage) Death and disability at 1 year is being collected
Notes	Trial terminated in September 1994 after 310 participants had been randomised on the advice of the Data Monitoring Committee due to an excess of cerebral haemorrhages and associated early mortality in the streptokinase-treated group Original sample size was to have been 600 participants The results included here are only for the first 270 participants (published in the *Lancet* in January 1995); the full results on the 310 participants cannot be included until the trial has been published in full Note the frequent use of heparin (25%) and aspirin (13.5%) within 24 hours of trial treatment and during the first 2 weeks (65% and 25% respectively)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

MAST-I 1995

Methods	Randomised controlled trial with 2 x 2 factorial design Central telephone randomisation Intention-to-treat Control group did not receive a placebo but 6-month follow-up was by blinded investigators

MAST-I 1995 *(Continued)*

Participants	All people with acute ischaemic strokes that could be randomised and start treatment within 6 hours from symptom onset; age > 18 years, but no upper limit; pre-entry CT mandatory to exclude cerebral haemorrhage Exclusions: rapidly improving symptoms likely to be a TIA; recent trauma or surgery; oral anticoagulant treatment (not aspirin); aspirin or streptokinase not either definitely indicated or definitely contraindicated; streptokinase in the past year, etc
Interventions	Streptokinase 1.5 MU i.v. over 1 hour immediately after randomisation, or aspirin 300 mg oral started immediately and continued for 10 days (or via nasogastric tube, per rectum, or i.v. in Italy), or both, or neither Other anticoagulants to be avoided within the first 24 hours, but could be used thereafter Aspirin use encouraged after 10 days or at hospital discharge (whichever came first)
Outcomes	Death within the first 10 days; cerebral haemorrhage; death and disability at 6 months (Rankin scale: disabled = Rankin 3 or more) 1-year follow-up is also being performed
Notes	Trial suspended after 622 participants randomised because of slow randomisation rate, partly due to increasing confusion about thrombolysis in stroke from ASK 1996 and MAST-E 1996

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

MELT 2007

Methods	PROBE: Prospective Randomised Open control study with Blinded Endpoint assessment; RCT Location: multi-centre, 57 centres in Japan; ongoing January 2002 to October 2005 Method of randomisation: Internet-based in 2 steps: - Step 1: pre-registration of all eligible people to angiography - Step 2: allocation to treatment or control Intention-to-treat
Participants	Eligibility and randomisation: - Step 1: all eligible people 20 - 75 years with clinical presentation of an MCA lesion possibly embolic, NIHSS 5 to 22, CT normal or with only subtle early ischaemic changes where angiography revealed complete occlusion of the horizontal M1 segment or the M2 division of the MCA proceed to randomisation - Step 2: treatment allocation Age limits: 20 - 75 years NIHSS > 5 Time window: 0 to 6 hours Participants: - Treatment group: male: 64.9%, age mean ± SD: 66.9 years (± 9.3), NIHSS: 14 (IQR 8), time from onset to allocation minimum 68 ± 61, occlusion location MCA M1: 68%, M2: 32% - Control group: male: 64.9%, age mean ± SD: 67.3 ± 8.5, NIHSS: 14 (IQR 7), time from onset to allocation minimum: 206 ± 54, occlusion location MCA M1: 74%, M2: 26% Previous lacunar infarcts allowed if no sequels Number randomised: 114 (treatment group 57; control group 57)
Interventions	UK i.a. infusion (treatment group) or conventional treatment (control group) After allocation treatment group immediate i.v. heparin (5000 IU) infusion An infusion catheter with a single end hole was then passed through the clot and positioned on the distal side of the thrombus if possible

MELT 2007 *(Continued)*

	More proximal regional infusion than inside the clot was prohibited Mechanical disruption of clots was permitted with the guidewire Repeat CT at maximum intervals of 2 hours was required and only in the absence or with subtle early ischaemic signs was the next step accepted: i.a. infusion of UK (120,000 IU over 5 minutes) This was repeated until a total dose of 600,000 IU; 2 hours had passed; or complete re-canalisation was achieved Control group: no specific treatment, osmotic diuretics in participants manifesting high intracranial pressure Neither group was allowed fibrinolytic therapy or antithrombotics (heparin, aspirin, ticlopidine) for 24 hours after fibrinolysis in the treatment group
Outcomes	Clinical outcome: NIHSS, mRS, BI at 7, 30 and 90 days after symptom onset (by blinded physician) Follow-up CT was scheduled at 24 hours, 7 and 90 days after symptom onset SICH was defined according to NINDS 1995 but also included participants with < 4 points on NIHSS in case of 'apparent signs considered as symptomatic' Follow-up angiography only in the treatment group and re-canalisation was evaluated by a blinded Film Reading Committet as: no, partial (≥ 50%), or complete re-canalisation
Notes	The trial was prematurely stopped upon advice from the Independent Monitoring Committee when i.v. rt-PA was approved for ischaemic stroke in October 2005

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

Mori 1992

Methods	Double-blind RCT Identical coded drug prepacks Not intention-to-treat
Participants	Ischaemic stroke in carotid territory < 6 hours from onset, aged < 80 years, pre-entry CT (to exclude haemorrhage) and angiography (to confirm arterial occlusion) Excluded: people in deep coma
Interventions	Duteplase (Sumitomo Pharmaceuticals, Tokyo) 20 or 30 MIU versus identical placebo i.v. over 1 hour The 20 and 30 MIU groups were analysed as 1 group in this review, i.e. the comparison is 'any duteplase versus placebo'
Outcomes	Reperfusion at 60 minutes after start of infusion, clinical status at 30 days using modified Hemispheric Stroke Scale (HSS) CT at 1, 2, 7 and 30 days for haemorrhagic transformation
Notes	Additional information from Prof Mori Unbalanced numbers due to accidental loss of a 20 MIU dose pack and substitution with placebo No participants excluded, therefore an ITT analysis was possible

Morris 1995

Methods	Double-blind, randomised trial of streptokinase 1.5 MU or placebo Randomisation method not stated (sequentially number drug prepacks probably) Intention-to-treat

Morris 1995 *(Continued)*

	Note saline is not an identical placebo for streptokinase
Participants	Anterior circulation acute ischaemic stroke that could be randomised and start treatment within 6 hours of onset (CT mandatory to exclude any haemorrhage), aged 40 - 80 years, no previous stroke
Interventions	Streptokinase 1.5 MU i.v. over 1 hour versus saline placebo
Outcomes	Death at 3 months, neurological improvement at 3 months, ICH
Notes	No additional information forthcoming from the authors

NINDS 1995

Methods	Randomised, placebo-controlled, blinded trial On-treatment analysis, not intention-to-treat Randomisation was at the participating hospital by sequentially numbered drug (or identical-looking placebo) prepacks, followed within 2 hours by a telephone call to the Trial Co-ordinating centre to notify them that an individual had been randomised
Participants	People with ischaemic stroke (CT mandatory to exclude ICH) with a clearly defined time of symptom onset who could receive the trial treatment within 180 minutes of symptom onset; age > 18 and < 80 years initially (80-year age limit removed on 30 March 1992 after 188 participants had been entered in Part A; a neurological deficit measurable on the NIH stroke scale (i.e. not very mild and not improving rapidly at the time of assessment) - thus cortical and lacunar strokes were eligible. People with previous stroke or head trauma within 3 months, pregnancy/lactation, abdominal surgery, heparin within 48 hours or deranged clotting factors/platelets, systolic BP > 180 or diastolic BP > 110 (+ various other features) were excluded
Interventions	Alteplase (rt-PA, Activase, Genentech, South San Francisco) in a dose of 0.9 mg per kg body weight (maximum dose 90 mg) or identical-looking placebo (prepared by Genentech) given i.v. The first 10% of the dose was given as a bolus followed by the remainder as a constant infusion over 60 minutes No antiplatelet or anticoagulants were to be given during the first 24 hours after randomisation, and BP had to be kept within prespecified limits (< 180 systolic and < 110 diastolic) The participants randomised within the first 90 minutes after the stroke were analysed separately from those randomised between 91 and 180 minutes after the stroke in the publication but have been put together in this review
Outcomes	Assessment was by a physician who had not been involved in the randomisation or treatment administration using the following: NIH stroke scale at 2 hours after start of treatment, and at 24 hours, 7 to 10 days and 3 months after onset of the stroke Glasgow outcome score at 3 months Barthel Index at 7 to 10 days and 3 months modified Rankin score (0 = no symptoms, 5 = severe disability) at 7 to 10 days and 3 months CT scan at 24 hours, 7 to 10 days and 3 months Rankin 2 or worse was the cut-off for disability in the analysis The data cannot be subdivided further at this point as the results have not yet been published by individual Rankin group
Notes	The trial was conducted in 2 phases: the first (291 participants) was to assess the effect of tPA on outcome at 24 hours after the stroke; the second (333 participants) was to assess the effect of tPA on outcome at 3 months The investigators remained blinded to the results of Part 1 until the end of Part 2 The protocols were identical for the 2 parts except for their primary hypotheses, i.e. participants in Part 1 were followed up at the same time points as in Part 2

NINDS 1995 *(Continued)*

	Additional information to that published is being sought from the principal investigators, but has not yet been received

Ohtomo 1985

Methods	Double-blind, randomised trial Identical prepacked drugs Not intention-to-treat
Participants	Presumed 'non-embolic' ischaemic stroke < 5 days, no age limit, pre-entry CT
Interventions	UK 60,000 U/day i.v. over 1 hour for 7 days versus identical-looking placebo UK supplied by Abbott Labs, USA
Outcomes	Clinical status (Global Improvement and Severity Ratings) and safety (absence of side effects) at 4 weeks from start of treatment Follow-up CT to assess haemorrhagic transformation
Notes	Additional information from Prof Ohtotmo All cases accounted for including those who 'dropped out'; therefore, an intention-to-treat analysis possible

PROACT 1998

Methods	Double-blind, placebo-controlled trial Centralised randomisation Follow-up blinded to treatment allocation by an independent neurologist who was blinded to the angiogram findings and in-hospital course
Participants	People aged 18 - 85 years without prior stroke, within 6 hours of onset of symptoms indicative of an MCA occlusion, NIHSS score > 4 and < 30, and who had an MCA occlusion (complete or major branch) on conventional intra-arterial angiography
Interventions	Recombinant prourokinase 6 mg or saline placebo i.a. through the angiogram catheter with the tip in the thrombus; heparin was also administered in a high dose to the first 16 participants, and thereafter in a lower dose, so the study was confounded Funding and drug supplied by Abbott Laboratories
Outcomes	Recanalisation of the MCA at 120 minutes after treatment infusion NIHSS, Barthel, Rankin, at 7, 30 and 90 days after treatment Haemorrhagic transformation of the infarct Extracranial bleeding Death
Notes	This trial was confounded by heparin (the dose of which was altered half way through the trial, and was testing i.a. not i.v. thrombolysis It has been included in the present data tables, though in a separate subgroup, until further information on i.a. thrombolysis becomes available to make a separate review worthwhile

Risk of bias

Bias	Authors' judgement	Support for judgement

PROACT 1998 *(Continued)*

Allocation concealment (selection bias)	Low risk

PROACT 2 1999

Methods	Randomised controlled trial Central telephone randomisation No placebo Follow-up assessment by a neurologist blinded to the angiogram result, treatment allocation, and to the in-hospital course, who was not involved in the care of the participant during the acute treatment phase Analysis was by intention-to-treat
Participants	People with acute ischaemic stroke, aged 18 - 85 years, with NIH stroke scale ≥ 4 but < 30, without visible infarction in > ⅓ of the MCA territory on baseline CT scan, with angiography-proven MCA main stem (M1) or major branch (M2) occlusion, within 6 hours of onset of stroke symptoms Randomisation stratified by stroke severity according to the baseline NIH Stroke Scale, and 2 participants allocated to active treatment for every 1 allocated control
Interventions	Pro-urokinase (Abbott Laboratories) 9 mg given i.a. through the angiography catheter with the tip embedded in the thrombus No placebo Heparin 2000 IU bolus i.v. at time of angiography followed by 500 IU/hour i.v. for 4 hours, to both treatment groups
Outcomes	Rankin ≤ 2 (i.e. independent) at 90 days after treatment, Rankin < 2 at 90 days, total deaths at 90 days, SICH, recanalisation (according to the TIMI classification for coronary occlusions) as documented on angiography at 2 hours after the start of the trial infusion
Notes	During the trial 12,323 people were screened, of whom 476 underwent angiography and only 180 were randomised

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

Wang 2003

Methods	RCT Location: Beijing Emergency Medical Centre and Statistical Department, Peking University, Beijing, China Method of randomisation: unclear 3 parallel groups: 2 doses and 1 control Single-centre trial Analysis: intention-to-treat
Participants	Eligibility: those eligible were divided into 3 groups Age limit: 35 - 80 years NIHSS: not defined Time window: 0 to 6 hours Participants: Chinese study population; BP 180/100 mmHg

Wang 2003 *(Continued)*

	Treatment group A: rt-PA 0.9 mg/kg, N = 34 Treatment group B: rt-PA 0.7 mg/kg, N = 33 Treatment group C: control, N = 33 CT: to rule out ICH or low-density lesion but not early ischaemic changes Number randomised: 100 (treatment group 67; control group 33)
Interventions	Actilyse (t-PA) 0.9 mg/kg to a maximum dose of 90 mg (Boehringer Ingelheim Germany) Treatment group A: 0.9 mg/kg Treatment group B: 0.7 mg/kg In both groups 8 mg rt-PA was injected i.v. as a bolus and the rest was given over 60 minutes to a maximum dose of 90 mg Control group: no thrombolytic therapy
Outcomes	Clinical: CSS (Chinese Stroke Scale) BI at 24 hours and 90 days Mortality at 30 days CT: 12 and 24 hours, 7 and 30 days Primary outcome: neurological and functional status, mortality, safety (ICH)
Notes	Same group of participants seem to have been included in Wang 2006 and Zeng 2006 but with more added; awaiting further assessment of these later publications

APTT = activated partial thromboplastin time
BI: Barthel Index
BP: blood pressure
CT: computed tomography
DWI: diffusion weighted imaging
GCS: Glasgow Coma Score
i.a.: intra-arterial
ICA: internal carotid artery
ICH: intracranial haemorrhage
INR: measure of anticoagulation in blood used to monitor warfarin dose
IQR: interquartile range
ITT: intention-to-treat
i.v.: intravenous
LOCF: last observation carried forward
M1, M2: different segments of the middle cerebral artery
MCA: middle cerebral artery
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
MTT: mean transit time
MU: mega units
NIH: National Institutes of Health
NIHSS: National Institutes of Health Stroke Scale
PCA: posterior cerebral artery
PWI: perfusion imaging
RCT: randomised controlled trial
rPRO-UK: recombinant pro-urokinase
rt-PA: recombinant tissue plasminogen activator
SICH: symptomatic intracranial haemorrhage
SITS-MOST: Safe Implementation of Thrombolysis in Stroke Monitoring Study
TIA: transient ischaemic attack
TIMI: thrombolysis in myocardial infarction, and was an angiographic scale developed to quantify arterial patency in the coronary arteries, now adapted to the intracranial arteries for stroke
Tmax: a method of quantifying a cerebral perfusion abnormality
tPA: tissue plasminogen activator
UK: urokinase

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

Study	Reason for exclusion
Bao 2003	Not randomised; no relevant outcomes
Boehringer Mannheim 1994	Study never started
CLEAR 2008	Low versus high dose of rt-PA
Davalos 2003	Not a RCT: observational study of DWI/PWI mismatch
Defuse 2001	Not a RCT: all participants received rt-PA
DeWinter 1999	Not relevant
Ding 2006	Not clearly randomised; comparison of lumbrokinase with control; latest outcome 28 days
Ducrocq 2005	Urokinase i.a. versus i.v.
EAST II [pers comm] 1999	EAST = pilot, open-dose escalation trial of a modified i.v. t-PA EAST II = RCT of same agent but stopped prematurely at very early stage due to unexpectedly high SICH rate
Edinburgh 1991	This study terminated prematurely because of the impracticality of i.a. thrombolytic treatment 4 participants were randomised between streptokinase (250,000 MU into the occluded cerebral artery) or placebo during the year that the trial ran (1991). It had been intended to randomise at least 10 participants; however, only 3 received streptokinase, 1 placebo. 1 (streptokinase) died within a week of the stroke of a massive cerebral infarct; 6-month outcome in the other 3 was: 1 (streptokinase) Rankin 2; 1 (streptokinase) Rankin 3; 1 (placebo) Rankin 4 These results have not been included because the number is so small and the randomisation (because of the premature termination) so imbalanced
EMFATAS 1996	Abandoned
EMS 1996	rt-PA i.a. plus i.v. versus i.v.
Fan 2001	Not a thrombolytic drug; fibrinolysis-enhancing only
Fisher 2003	Not a RCT
Fu 2004	No SICH, death or poor functional outcome data at all and discrepancies in dose of drug and low-dose urokinase for 5 days starting > 24 hours
Fuentes 2007	Non-random case series
Geng 2004	Confounded by heparin
Hartmann 2005	Abstract only; author did not respond to multiple requests for more information between October 2007 and December 2008; no evidence that randomised comparison of rt-PA
Hong Kong 1994	This trial of i.v. streptokinase, stopped prematurely after randomisation of only a few participants because of concerns about use of streptokinase arising from termination of ASK 1996, MAST-E 1996 and MAST-I 1995
Huang 1996	Snake venom; not a thrombolytic agent

Study	Reason for exclusion
Huang 2000	Trial of lumbrokinase; effect on blood coagulability; no neurological outcomes mentioned; no detail of control groups
ICTuS-L 2006	Interventional clot-pulling trial
IMS II 2004	Non-random single arm pilot
IMS III 2008	rt-PA i.v. versus i.a.
INSTINCT 2005	Trial of modifying physician attitudes, not of rt-PA
ITAIS 2005	Not a RCT; using multimodal MRI to decide whether to give i.a. or i.v. rt-PA
Jin 2000	Trial of effect of lumbrokinase on blood coagulability; no neurological outcome measures; further details awaited
Kandil 2001	Only ever published in abstract, insufficient details, apparently RCT of i.a. urokinase plus heparin versus heparin in 36 participants; no clinical details
Kim 2008	Non-random case series
Konta 1996	Comparison of 2 doses of urokinase, not clear if random
Lang 2013	Not a trial of thrombolysis; is a trial of cerebrolysin in participants already treated with rt-PA
Li 2003	Urokinase versus acupuncture, not clear that it is a RCT, only recorded SICH; no information on death or dependency
Lindsberg 2006	Non-random, observational comparison of i.v. and i.a. rt-PA in basilar artery occlusion
Liu 1991	Urokinase and dextran i.v. versus i.a. and dextran
Liu 1994	RCT of ahylysantifarctase once per day for 21 days plus dextran versus dextran, i.v. administration, outcome measures were all of changes in blood coagulation not neurological assessments; no mention of cerebral haemorrhages or deaths
Liu 2004	No long-term follow-up (latest at 4 weeks), no functional outcome
Lu 2001	Not a RCT, only information on blood fibrinogen levels
Lyden 2003a	Non-random, dose-escalating study of tenekteplase
Lyden 2003b	rt-PA +/- hypothermia; not trial of rt-PA
Meyer 1963	Although randomised and controlled, this trial was conducted in the pre-CT era and therefore there was no way of being sure that only people with ischaemic stroke were included
Meyer 1964	Although randomised and controlled, this trial was conducted in the pre-CT era and therefore there was no way of being sure that only people with ischaemic stroke were included
Michel 2008	Small randomised feasibility study with PCT for participant selection - stopped as unfeasible
MITI-IV 2005	Not a thrombolytic drug
Molina 2005	Trial of microbubble-enhanced sonothrombolysis in the presence of rt-PA, i.e. not a trial of rt-PA

Study	Reason for exclusion
Morris 2002	Not relevant
Naito 1984	The data are presented in 2, possibly 3, different publications; many participants were lost to follow-up during the 4-week trial period. Dr Naito has died and Professor Abe is unable to supply further information on those lost to follow-up. Although there were no deaths or cerebral haemorrhages among the participants who completed the 4-week trial period, the data are incomplete and may be badly skewed by lack of information on what happened to the participants who dropped out
Ohta 1997	Non-random case series
Pan 2011	Not a randomised trial - just an observational study
Pang 1993	Appears to be a randomised trial (method uncertain) of lumbrokinase 2 tablets daily for 21 days versus placebo; 303 participants received lumbrokinase and 150 participants received placebo, both groups received dextran; very little known about outcome. Follow-up was at 3 weeks only, therefore this trial was excluded. No information on deaths or intracranial haemorrhages. There is thought to have been conflict between the authors and the pharmaceutical sponsor so no further details have been published (Liu M, personal communication)
PRACTISE 2005	Trial of implementation of rt-PA, not of rt-PA itself
Qiang 2001	Not a RCT; study of DWI/PWI
Qureshi 2001	Not relevant
Qureshi 2006	Reteplase and abciximab dose escalation; no control
Ribeiro 2012	Not a trial
ROSIE 2002	Reteplase dose escalation
ROSIE-2 2002	
ROSIE-CT 2002	Non-randomised, dose-escalation of abciximab versus reteplase + abciximab
Rother 2003	DWI/PWI comparison, not a RCT
Shi 2000	Not a RCT; no relevant outcomes
Skoloudik 2004	Not a RCT; ultrasound versus no ultrasound in presence of rt-PA
Skoloudik 2006	Not a RCT; ultrasound versus no ultrasound in presence of rt-PA
Sobrino 2007	Non-random dose study of endothelial cells
SYNTHESIS 2007	Comparison of i.v. versus i.a. rt-PA within 3 hours of stroke
TEMPO 2013	Trial of tenecteplase versus rt-PA in minor stroke
TNK 2005	Dose escalation study
TNK-S2B 2005	RCT of 3 doses of tenecteplase versus rt-PA
TNK-TPA 2008	Tenecteplase versus tPA

Study	Reason for exclusion
Trouillas 2000	Not a RCT; haematological study of effect of rt-PA on clotting factors
TTATTS 1997	Dose-range-finding study of rt-PA on recanalisation in people with angiographic evidence of arterial occlusion; never published in full. Not a RCT
VASTT 2005	Dose-range-finding comparison of rt-PA variant V10153; same as Vernalis 2005
Vernalis 2005	Dose-range-finding comparison of rt-PA variant V10153; same as VASTT 2005
Wang 1997	Blood results only
Wang 1999	Ahylysantinfactase versus defibrase
Xiang 1995	Randomised trial (method unknown) of i.a. urokinase 300,000 to 1,000,000 units for 1 hour plus heparin, plus a 'physical therapy' (nature uncertain) plus 'conventional treatment' versus 'conventional treatment' (nature uncertain) started within 6 hours of onset of acute ischaemic carotid territory stroke. 67 participants were included, 32 in the active and 35 in the placebo arms. Follow-up was at 3 months using a neurological deficit score. The number of deaths and intracranial haemorrhages was not mentioned. The trial was excluded because of the confounding of treatment allocation
Xu 1997	No details of control group and not conventional drug regimen
Xu 2000	No placebo
Xu 2004	Urokinase and nimodipine
Yuan 1995	A randomised trial of i.v. urokinase 8000 to 10,000 u/kg (total 600,000 to 900,000) plus nimodipine, vitamins E and C, aspirin, mannitol, dexamethasone, nidocain and snake venom, versus 'conventional treatment' (i.e. everything except urokinase) given over 40 minutes within 2 days of onset of ischaemic stroke; urokinase 10,000 to 15,000 repeated the following day if no improvement. Follow-up was using the Chinese Neurological Scale at only 2 weeks after treatment; no long-term follow-up. This scale does not appear to measure dependency. A total of 80 participants were randomised, 40 per treatment arm. There is no mention of the number who died or had SICH. The trial was excluded because of the short follow-up period
Zhang 2003	No dependency data, odd dose of urokinase
Zhou 1996	Not a RCT; drug unclear; only measured endothelial function

CT: computed tomography
DWI: diffusion weighted imaging
i.a.: intra-arterial
i.v.: intravenous
MRI: magnetic resonance imaging
MU: mega units
PCT: perfusion computed tomography
PWI: perfusion imaging
RCT: randomised controlled trial
rt-PA: recombinant tissue plasminogen activator
SICH: symptomatic intracranial haemorrhage
tPA: tissue plasminogen activator

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

FRALYSE

Methods	Data awaited
Participants	Data awaited
Interventions	Data awaited
Outcomes	Data awaited
Notes	Data awaited

Lin 2006

Methods	RCT
Participants	46 to 72-year-old participants within 6 hours of acute ischaemic stroke CT
Interventions	Urokinase 1,500,000 U over 40 minutes in i.v. versus control (no placebo)
Outcomes	SICH, death, activities of daily living scale (sounds like mRS) at 6 months
Notes	95 participants; further translation required

TESPI

Methods	RCT
Participants	Age > 80 years, < 3 hours of acute ischaemic stroke, NIHSS upper limit 17
Interventions	I.v. rt-PA as per NINDS dose versus placebo
Outcomes	Uncertain
Notes	Planned sample size 600 total

CT: computed tomography
i.v.: intravenous
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
RCT: randomised controlled trial
rt-PA: recombinant tissue plasminogen activator
sc: subcutaneous
SICH: symptomatic intracranial haemorrhage

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

BASICS

Trial name or title	BASICS
Methods	Intra-arterial and intravenous treatment

BASICS *(Continued)*

Participants	Basilar occlusion after i.v. rt-PA within 4.5 hours of stroke
Interventions	Urokinase, rt-PA, catheter devices
Outcomes	12-month mRS
Starting date	-
Contact information	-
Notes	Basically a trial of intra-arterial plus intravenous versus intravenous - probably relevant to Wardlaw 2013

DIAS-3

Trial name or title	Desmoteplase in Acute Stroke 3
Methods	Within 3 to 9 hours of onset
Participants	Acute ischaemic stroke selected on basis of advanced imaging
Interventions	Desmoteplase 90 microgrammes/kg i.v. as bolus versus placebo
Outcomes	90 days
Starting date	-
Contact information	-
Notes	Nearing completion

DIAS-4

Trial name or title	Desmoteplase in Acute Stroke 4
Methods	Within 3 to 9 hours of onset
Participants	Acute ischaemic stroke selected on basis of advanced imaging
Interventions	Desmoteplase 90 microgrammes/kg i.v. as bolus versus placebo
Outcomes	90 days
Starting date	-
Contact information	-
Notes	Nearing completion

DIAS-J

Trial name or title	Desmoteplase in Acute Stroke Japan
Methods	Within 3 to 9 hours of onset
Participants	Acute ischaemic stroke selected on basis of advanced imaging
Interventions	Desmoteplase 70 or 80 microgrammes/kg i.v. as bolus versus placebo
Outcomes	90 days
Starting date	-
Contact information	-
Notes	Nearing completion

EXTEND

Trial name or title	EXTEND
Methods	RCT of rt-PA at 3 - 6 and 6 - 9 hours after acute ischaemic stroke with specific lesion features
Participants	People with acute stroke with PWI:DWI 2:1, PWI lesion > 20 ml, Tmax 6 seconds, CTP if needed, NIHSS 4 to 26
Interventions	rt-PA i.v. dose as per NINDS 1995
Outcomes	Unclear
Starting date	Unclear - seeking funding
Contact information	-
Notes	Full trial would have 15% absolute risk reduction, 80% power, 0.05 alpha, allowing for 15% drop-out, need 200 per arm; 100-patient Australian and New Zealand pilot study

Ogawa ia Urokinase

Trial name or title	Intra-arterial urokinase trial
Methods	-
Participants	People with stroke due to MCA embolic occlusion within 6 hours; further information being sought
Interventions	Intra-arterial urokinase versus placebo
Outcomes	Unknown
Starting date	April 2002
Contact information	Prof Ogawa

Ogawa ia Urokinase *(Continued)*

	aogawa@iwate-med.ac.jp
Notes	-

PROACT III

Trial name or title	PROACT III
Methods	-
Participants	Further information awaited
Interventions	Unknown
Outcomes	Unknown
Starting date	Unknown
Contact information	Unknown
Notes	Believed withdrawn by pharmaceutical company (Abbott) and unlikely to start as at March 2003

WAKE-UP 2011

Trial name or title	Wake Up stroke
Methods	DWI-FLAIR mismatch to select participants for thrombolysis with acute ischaemic stroke without known time of onset
Participants	Acute ischaemic stroke with DWI-FLAIR mismatch
Interventions	rt-PA 9 mg/kg, 10% as bolus, rest over 1 hour
Outcomes	90 day mRS
Starting date	2013
Contact information	-
Notes	-

WASSABI

Trial name or title	WASSABI
Methods	Unknown
Participants	People who wake up with stroke

WASSABI *(Continued)*

Interventions	Unknown
Outcomes	Unknown
Starting date	Unknown
Contact information	-
Notes	Not much is known about this trial

Yamanouchi iv rt-PA

Trial name or title	Unknown
Methods	-
Participants	Unknown
Interventions	Intravenous rt-PA versus placebo
Outcomes	Unknown
Starting date	Unknown
Contact information	Unknown
Notes	-

CT: computed tomography
CTP: computed tomography perfusion
DWI: diffusion weighted imaging
FLAIR: fluid attenuated inversion recovery
i.a.: intra-arterial
i.v.: intravenous
MCA: middle cerebral artery
NIHSS: National Institutes of Health Stroke Scale
PWI: perfusion imaging
RCT: randomised controlled trial
rt-PA: recombinant tissue plasminogen activator
SICH: symptomatic intracranial haemorrhage
Tmax: a method of quantifying a cerebral perfusion abnormality

DATA AND ANALYSES

Comparison 1. Any thrombolytic agent versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths from all causes within 7 to 10 days	13	7458	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.69 [1.44, 1.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Intravenous urokinase versus control	1	465	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.35 [0.62, 2.94]
1.2 Intravenous streptokinase versus control	3	963	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.90 [1.37, 2.63]
1.3 Intravenous rt-PA versus control	8	5535	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [1.18, 1.76]
1.4 Intravenous streptokinase plus oral aspirin versus oral aspirin	1	309	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.86 [2.26, 6.59]
1.5 Intravenous desmoteplase versus control	1	186	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.73 [0.85, 26.26]
2 Fatal intracranial haemorrhage within 7 to 10 days	17	9066	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.53 [3.47, 5.91]
2.1 Intravenous urokinase versus control	2	751	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.43 [1.08, 18.18]
2.2 Intravenous streptokinase versus control	4	983	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.03 [3.47, 10.47]
2.3 Intravenous rt-PA versus control	8	6683	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.18 [2.99, 5.84]
2.4 Intravenous streptokinase plus oral aspirin versus oral aspirin	1	309	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.56 [1.62, 12.84]
2.5 Intra-arterial pro-urokinase plus intravenous heparin versus intravenous heparin	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.03, 9.65]
2.6 Intra-arterial urokinase versus control	1	114	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
2.7 Intravenous desmoteplase versus control	1	186	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.65 [0.58, 37.52]
3 Deaths within the first 7 to 10 days from causes other than fatal intracranial haemorrhage	10	7226	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.90, 1.30]
3.1 Intravenous urokinase versus control	1	465	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.35, 2.13]
3.2 Intravenous streptokinase versus control	3	963	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.72, 1.53]
3.3 Intravenous rt-PA versus control	5	5303	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.73, 1.18]
3.4 Intravenous streptokinase plus oral aspirin versus oral aspirin	1	309	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.13 [1.74, 5.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5 Intravenous desmoteplase versus control	1	186	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.57 [0.24, 86.20]
4 Symptomatic (including fatal) intracranial haemorrhage within 7 to 10 days	27	10186	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.75 [3.11, 4.51]
4.1 Intravenous urokinase versus control	4	1208	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.47, 3.48]
4.2 Intravenous streptokinase versus control	4	983	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.20 [3.25, 8.32]
4.3 Intravenous rt-PA versus control	12	7011	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.72 [2.98, 4.64]
4.4 Intravenous streptokinase plus oral aspirin versus oral aspirin	1	309	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.02 [1.55, 10.40]
4.5 Intra-arterial pro-urokinase plus intravenous heparin versus intravenous heparin	2	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.39 [0.88, 6.47]
4.6 Intra-arterial urokinase versus control	2	130	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.04 [0.79, 20.74]
4.7 Intravenous desmoteplase versus control	3	325	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.50 [1.37, 14.81]
5 Symptomatic (including fatal) cerebral oedema	6	5961	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.79, 1.19]
6 Death or dependency at the end of follow-up	22	9318	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.78, 0.93]
6.1 Intravenous urokinase versus control	1	465	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.64, 1.42]
6.2 Intravenous streptokinase versus control	4	983	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.72, 1.24]
6.3 Intravenous rtA versus control	10	6886	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.77, 0.93]
6.4 Intravenous streptokinase plus oral aspirin versus oral aspirin	1	309	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.69, 1.73]
6.5 Intra-arterial pro-urokinase plus intravenous heparin versus intravenous heparin	2	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.31, 1.00]
6.6 Intra-arterial urokinase versus control	2	130	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.57 [0.28, 1.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.7 Intravenous desmoteplase versus control	3	325	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.53, 1.40]
7 Deaths occurring between 7 and 10 days and the end of follow-up	13	7458	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.76, 1.02]
7.1 Intravenous urokinase versus control	1	465	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.05 [0.60, 6.99]
7.2 Intravenous streptokinase versus control	3	963	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.61, 1.26]
7.3 Intravenous rt-PA versus control	8	5535	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.71, 0.99]
7.4 Intravenous streptokinase plus oral aspirin versus control	1	309	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.49, 2.27]
7.5 Intravenous desmoteplase versus control	1	186	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.95 [1.37, 17.86]
8 Deaths from all causes during follow-up	27	10187	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [1.06, 1.30]
8.1 Intravenous urokinase versus control	4	1208	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.68, 1.97]
8.2 Intravenous streptokinase versus control	4	983	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [1.10, 1.88]
8.3 Intravenous rt-PA versus control	12	7012	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.94, 1.20]
8.4 Intravenous streptokinase plus oral aspirin versus oral aspirin	1	309	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.02 [1.87, 4.87]
8.5 Intra-arterial pro-urokinase plus intravenous heparin versus intravenous heparin	2	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.40, 1.42]
8.6 Intra-arterial urokinase versus control	2	130	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.34, 4.57]
8.7 Intravenous desmoteplase versus control	3	325	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.17 [0.97, 4.84]
9 Death or dependency defined as mRS 2 to 6	21	8824	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.70, 0.84]
9.1 Intravenous urokinase versus control	1	465	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.57 [0.38, 0.85]
9.2 Intravenous streptokinase versus control	4	983	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.61, 1.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3 Intravenous rt-PA versus control	10	6887	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.71, 0.88]
9.4 Intravenous desmoteplase versus control	2	139	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.28, 1.43]
9.5 Intra-arterial pro-urokinase versus control	2	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.32, 1.19]
9.6 Intra-arterial urokinase versus control	2	130	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.17, 0.77]
10 Death or dependency defined as mRS 3 to 6	21	8824	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.78, 0.93]
10.1 Intravenous urokinase versus control	1	465	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.67, 1.47]
10.2 Intravenous streptokinase versus control	4	983	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.72, 1.24]
10.3 Intravenous rt-PA versus control	10	6887	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.77, 0.94]
10.4 Intravenous desmoteplase versus control	2	139	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.22, 1.08]
10.5 Intra-arterial pro-urokinase versus control	2	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.31, 1.00]
10.6 Intra-arterial urokinase versus control	2	130	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.57 [0.28, 1.14]
11 Dependency at the end of follow-up defined as mRS 3 to 5	22	9318	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.69, 0.82]
11.1 Intravenous urokinase versus control	1	465	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.53, 1.22]
11.2 Intravenous streptokinase versus control	4	983	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.49, 0.85]
11.3 Intravenous rt-PA versus control	10	6886	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.73, 0.89]
11.4 Intravenous streptokinase plus oral aspirin versus oral aspirin	1	309	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.22, 0.58]
11.5 Intra-arterial pro-urokinase plus intravenous heparin versus intravenous heparin	2	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.72 [0.41, 1.28]
11.6 Intra-arterial urokinase versus control	2	130	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.53 [0.26, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.7 Intravenous desmoteplase versus control	3	325	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.41, 1.06]
12 Alive and independent (mRS 0 to 2) at end of follow-up, participants treated up to six hours	10	6887	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [1.06, 1.29]
13 Alive and favourable outcome (mRS 0 to 1) at end of follow-up, participants treated up to six hours	10	6887	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.29 [1.16, 1.43]
14 Deaths from all causes ordered by antithrombotic drug use	24	9674	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [1.08, 1.33]
14.1 All participants received antithrombotic drugs < 24 hours	6	2191	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [1.09, 1.58]
14.2 Some participants received antithrombotic drugs < 24 hours	4	1757	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.99, 1.63]
14.3 Some participants received antithrombotics but not < 24 hours	12	4670	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.96, 1.34]
14.4 No participants received antithrombotic drugs < 10 days	4	1056	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.58, 1.37]
15 Deaths from all causes ordered by stroke severity	27	9878	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [1.01, 1.25]
15.1 Case fatality 0% - 19% in the control group	17	4973	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [1.08, 1.58]
15.2 Case fatality 20% or greater in the control group	10	4905	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.92, 1.19]
16 Death or dependency at the end of follow-up: participants randomised within 3 hours of stroke	10	2160	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.56, 0.79]
16.1 Intravenous urokinase versus control	1	82	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.31, 2.00]
16.2 Intravenous streptokinase versus control	3	209	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.35, 1.09]
16.3 Intravenous rt-PA versus control	6	1779	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.65 [0.54, 0.80]
16.4 Intravenous streptokinase plus oral aspirin versus oral aspirin	1	90	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.40, 2.18]
17 Death or dependency by time to treatment up to 6 hours: all agents: only trials randomising in both 0 to 3 and 3 to 6 hour time windows	9	6941	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.83, 1.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Treatment within 3 hours	9	1536	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.55, 0.85]
17.2 Treatment between 3 and 6 hours	9	5405	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.88, 1.10]
18 Death or dependency by time to treatment up to 6 hours: rt-PA: only trials randomising in 0 - 3 and 3 - 6 hour windows	5	5204	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.80, 1.01]
18.1 Treatment within 3 hours	5	1155	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.53, 0.87]
18.2 Treatment between 3 to 6 hours	5	4049	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.85, 1.09]
19 Death or dependency by time to treatment up to 6 hours: rt-PA: all trials regardless of time window	8	6729	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.77, 0.94]
19.1 Treatment within 3 hours	6	1779	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.65 [0.54, 0.80]
19.2 Treatment between 3 and 6 hours	7	4950	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.83, 1.04]
20 Death or dependency by latest time to randomisation	22	9009	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.71, 0.92]
20.1 3 hours	1	624	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.45, 0.85]
20.2 4.5 hours	2	1161	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.66, 1.32]
20.3 6 hours	15	6883	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.69, 0.95]
20.4 9 hours	3	325	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.35, 1.59]
20.5 24 hours	1	16	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.01, 1.76]
21 Alive and independent (mRS 0 to 2) at end of follow-up, participants treated < 3 versus 3 to 6 hours, all trials regardless of latest time window	8	6750	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [1.06, 1.29]
21.1 Participants treated within three hours	6	1779	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [1.26, 1.86]
21.2 Participants treated 3 - 6 hours	7	4971	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.96, 1.20]

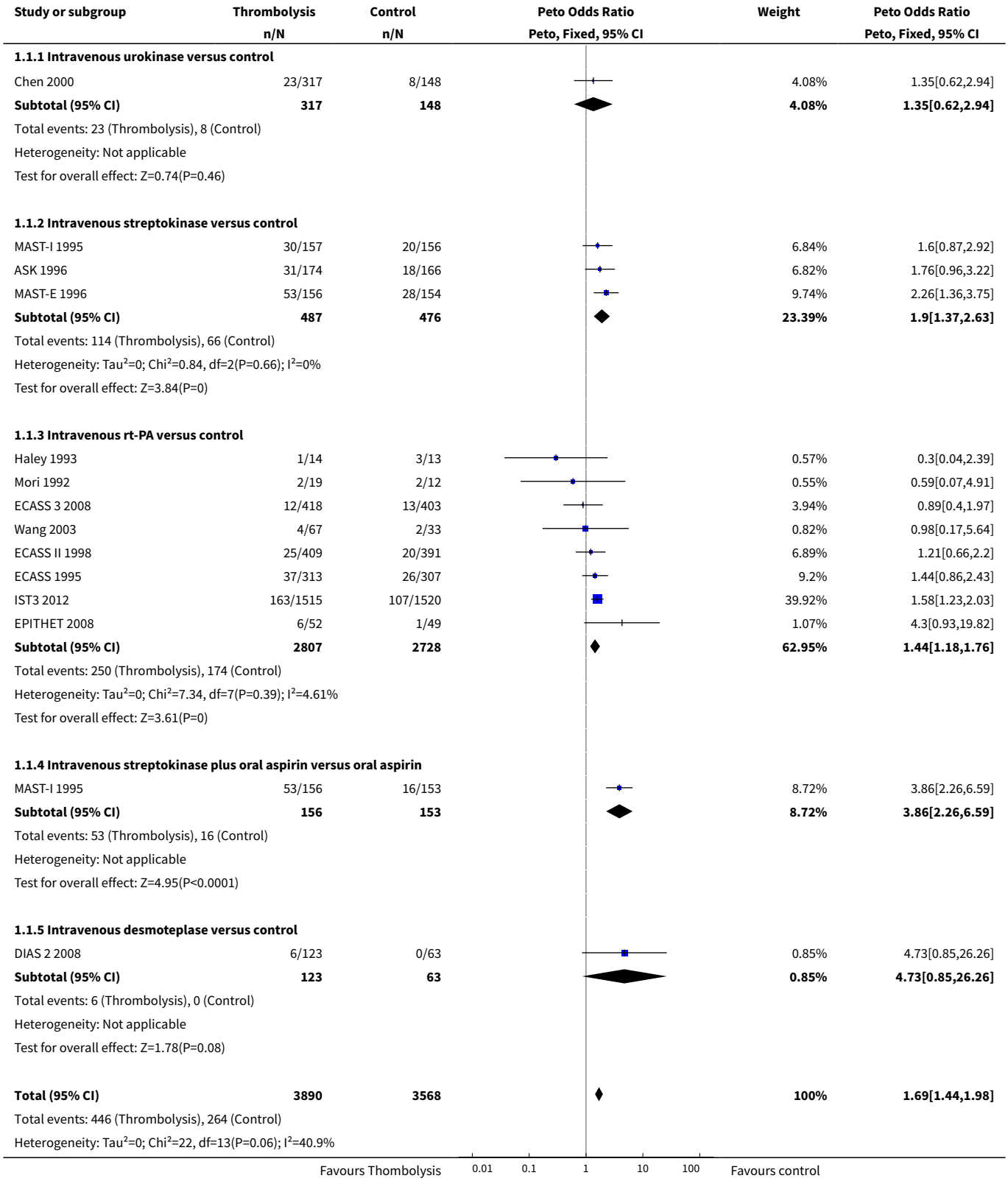
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22 Alive and favourable outcome (mRS 0 to 1) at end of follow-up, < 3 versus 3 - 6 hours, only trials randomising in both time windows	6	1779	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.61 [1.30, 1.99]
22.1 Participants treated < 3 hours	6	1779	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.61 [1.30, 1.99]
22.2 Participants treated 3 - 6 hours	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Deaths from all causes during follow-up: participants randomised within 3 hours of stroke	11	2187	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.82, 1.21]
23.1 Intravenous streptokinase versus control	3	209	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.66, 2.14]
23.2 Intravenous tPA versus control	7	1806	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.73, 1.13]
23.3 Intravenous streptokinase plus oral aspirin versus oral aspirin	1	90	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.37 [1.37, 8.26]
23.4 Intravenous urokinase versus control	1	82	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.14, 3.51]
24 Deaths by time to treatment up to 6 hours: all agents: only trials randomising in both 0 - 3 and 3 - 6 hour time windows	9	6936	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [1.10, 1.38]
24.1 Treatment within 3 hours	9	1536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.86, 1.35]
24.2 Treatment between 3 and 6 hours	9	5400	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.29 [1.13, 1.48]
25 Deaths by time to treatment up to 6 hours: rt-PA: only trials randomising in both 0 to 3 and 3 to 6 hour time windows	5	5199	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.97, 1.28]
25.1 Treatment within 3 hours	5	1155	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.75, 1.26]
25.2 Treatment between 3 and 6 hours	5	4044	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [1.00, 1.38]
26 Deaths by time to treatment up to 6 hours: rt-PA: all trials regardless of time window	9	6772	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.95, 1.21]
26.1 Treatment within 3 hours	7	1806	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.73, 1.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.2 Treatment between 3 and 6 hours	7	4966	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [1.00, 1.35]
27 Death by latest time to treatment	24	9039	Odds Ratio (Peto, Fixed, 95% CI)	1.12 [1.01, 1.25]
27.1 3 hours	2	651	Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.53, 1.17]
27.2 4.5 hours	2	1161	Odds Ratio (Peto, Fixed, 95% CI)	1.43 [1.01, 2.03]
27.3 6 hours	16	6886	Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.99, 1.26]
27.4 9 hours	3	325	Odds Ratio (Peto, Fixed, 95% CI)	2.10 [0.79, 5.58]
27.5 24 hours	1	16	Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.14, 7.10]
28 Symptomatic intracranial haemorrhage by time to treatment up to 6 hours: rt-PA: only trials randomising in both 0 - 3 and 3 - 6 hour time windows.	5	5168	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.75 [2.94, 4.78]
28.1 Intravenous rt-PA versus control: participants treated within 3 hours of stroke	5	1155	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.25 [2.53, 7.16]
28.2 Intravenous rt-PA versus control: participants treated between 3 and 6 hours after stroke	5	4013	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.62 [2.76, 4.76]
29 Symptomatic intracranial haemorrhage by time to treatment up to 6 hours: rt-PA: all trials regardless of time window	8	6714	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.93 [3.13, 4.93]
29.1 Intravenous rt-PA versus control: participants treated within 3 hours of stroke	6	1779	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.55 [2.92, 7.09]
29.2 Intravenous rt-PA versus control: participants treated between 3 and 6 hours after stroke	7	4935	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.73 [2.86, 4.86]
30 Symptomatic intracranial haemorrhage by latest time to treatment	23	9104	Odds Ratio (Peto, Fixed, 95% CI)	4.41 [3.43, 5.69]
30.1 3 hours	2	651	Odds Ratio (Peto, Fixed, 95% CI)	5.85 [1.54, 22.26]
30.2 4.5 hours	2	1161	Odds Ratio (Peto, Fixed, 95% CI)	6.56 [2.51, 17.18]

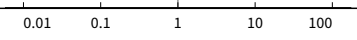
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30.3 6 hours	15	6951	Odds Ratio (Peto, Fixed, 95% CI)	4.20 [3.21, 5.50]
30.4 9 hours	3	325	Odds Ratio (Peto, Fixed, 95% CI)	6.82 [0.88, 52.78]
30.5 24 hours	1	16	Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
31 Death or dependency (mRS 3 to 6) by the end of follow-up; participants treated up to 6 hours aged ≤ 80 years versus > 80 years	10	6871	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.76, 0.93]
31.1 Participants aged ≤ 80 years	10	5175	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.76, 0.95]
31.2 Participants aged > 80 years	3	1696	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.64, 0.99]
32 Death or dependency (mRS 3 to 6) by the end of follow-up, participants treated within 3 hours aged ≤ 80 years versus > 80 years	6	1765	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.51, 0.76]
32.1 Participants aged ≤ 80 years	6	1039	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.52, 0.85]
32.2 Participants aged > 80 years	2	726	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.40, 0.78]
33 Alive and independent (mRS 0 to 2) at end of follow-up, participants treated up to 6 hours aged ≤ 80 years versus > 80 years	10	6885	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [1.07, 1.31]
33.1 Participants aged ≤ 80 years	10	5174	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [1.05, 1.31]
33.2 Participants aged > 80 years or over	3	1711	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.98, 1.52]
34 Alive and independent (mRS 0 to 2) at end of folllow-up, participants treated within 3 hours, aged ≤ 80 years versus > 80 years	6	1779	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [1.28, 1.90]
34.1 Participants aged ≤ 80 years versus	6	1038	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [1.18, 1.92]
34.2 Participants aged > 80 years and over	2	741	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [1.20, 2.34]
35 Alive and independent (mRS 0 to 2) at end of follow-up, participants treated	7	4971	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.96, 1.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 - 6 hours, aged ≤ 80 years versus > 80 years				
35.1 Participants aged ≤ 80 years	7	4001	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.96, 1.24]
35.2 Participants aged > 80 years	2	970	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.73, 1.30]
36 Death: selection by MR DWI/PWI or CT	19	8760	Odds Ratio (Peto, Fixed, 95% CI)	1.14 [1.02, 1.27]
36.1 Plain CT	15	8334	Odds Ratio (Peto, Fixed, 95% CI)	1.12 [1.00, 1.25]
36.2 MR DWI/PWI	4	426	Odds Ratio (Peto, Fixed, 95% CI)	2.05 [1.02, 4.15]
37 Death or dependency: selection with MR DWI/PWI versus plain CT	15	8268	Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.74, 0.89]
37.1 Selection with plain CT	11	7843	Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.73, 0.89]
37.2 Selection with MR DWI/PWI	4	425	Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.58, 1.35]
38 Symptomatic intracranial haemorrhage: selection with MR DWI/PWI or CT	20	8784	Odds Ratio (Peto, Fixed, 95% CI)	4.44 [3.43, 5.75]
38.1 Plain CT	16	8358	Odds Ratio (Peto, Fixed, 95% CI)	4.38 [3.38, 5.69]
38.2 MR DWI/PWI	4	426	Odds Ratio (Peto, Fixed, 95% CI)	7.51 [1.40, 40.35]
39 Alive and independent (mRS 0 to 1) at end of follow-up, by plain CT ASPECTS score	4	4567	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [1.07, 1.37]
39.1 ASPECTS score 8 - 10	4	3317	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [1.06, 1.39]
39.2 ASPECTS score 0 - 7	4	1250	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.91, 1.58]
40 Death or dependency at the end of follow-up: intra-arterial thrombolysis versus control	4	350	Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.31, 0.79]
40.1 Intra-arterial urokinase versus control	2	130	Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.22, 0.91]
40.2 Intra-arterial pro-urokinase versus control	2	220	Odds Ratio (Peto, Fixed, 95% CI)	0.53 [0.28, 1.00]

Analysis 1.1. Comparison 1 Any thrombolytic agent versus control, Outcome 1 Deaths from all causes within 7 to 10 days.



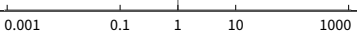
Study or subgroup	Thrombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Test for overall effect: Z=6.5(P<0.0001)					
Test for subgroup differences: Chi²=13.82, df=1 (P=0.01), I²=71.05%					



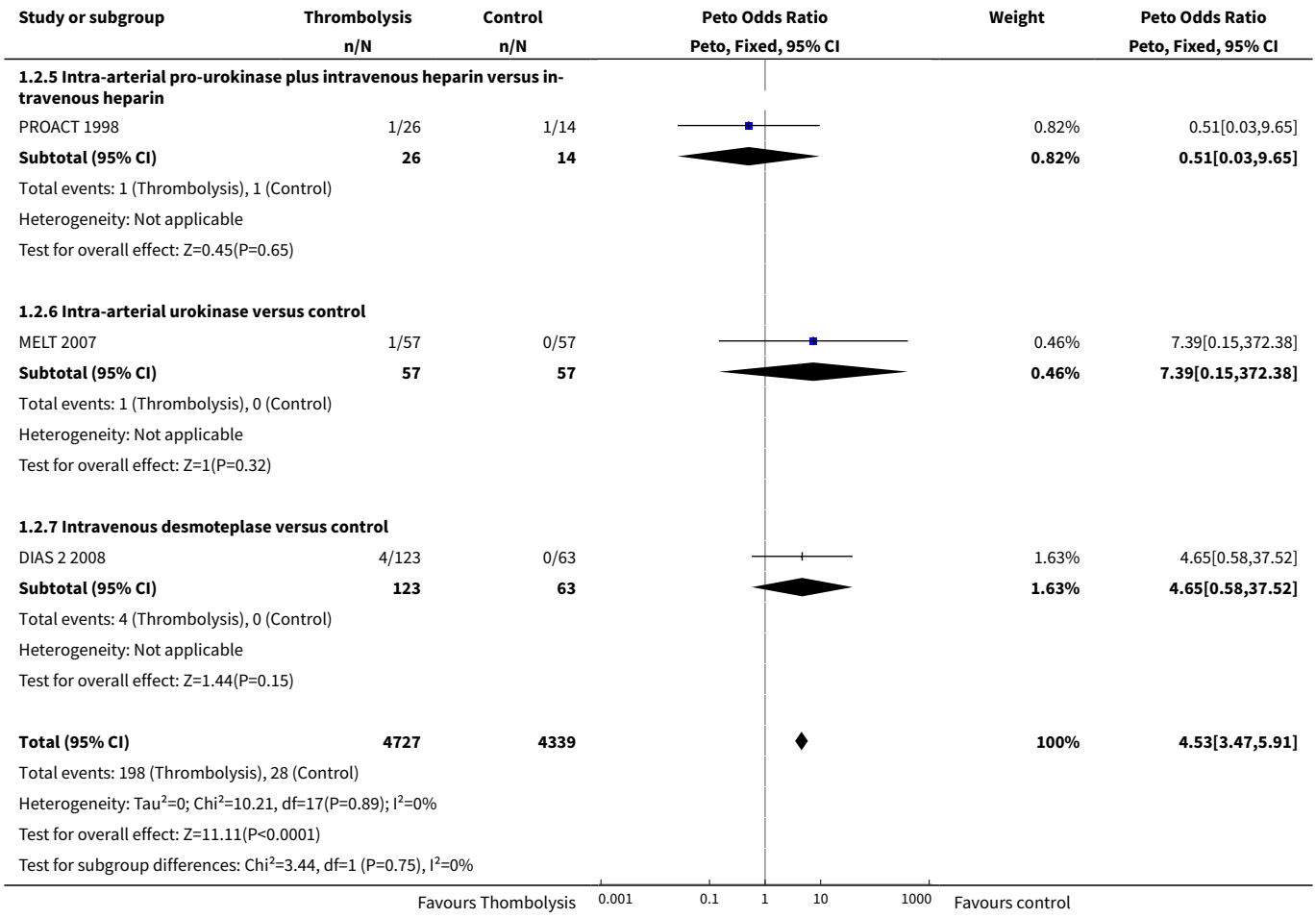
Favours Thombolysis — Favours control

Analysis 1.2. Comparison 1 Any thrombolytic agent versus control, Outcome 2 Fatal intracranial haemorrhage within 7 to 10 days.

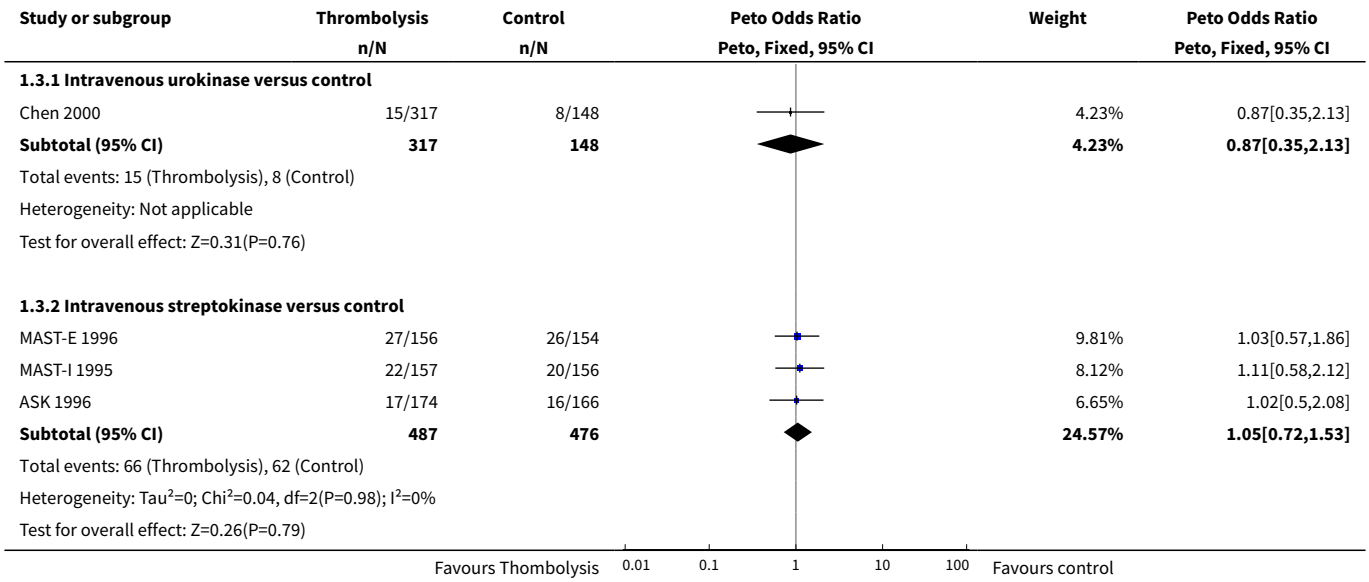
Study or subgroup	Thrombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.2.1 Intravenous urokinase versus control					
Atarashi 1985	1/192	0/94		0.41%	4.44[0.07,287.76]
Chen 2000	8/317	0/148		3.16%	4.43[0.99,19.85]
Subtotal (95% CI)	**509**	**242**		**3.57%**	**4.43[1.08,18.18]**
Total events: 9 (Thrombolysis), 0 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%					
Test for overall effect: Z=2.07(P=0.04)					
1.2.2 Intravenous streptokinase versus control					
Morris 1995	2/10	0/10		0.88%	8.26[0.48,142.43]
MAST-E 1996	26/156	2/154		11.81%	6.45[2.97,14.01]
MAST-I 1995	8/157	0/156		3.62%	7.69[1.89,31.22]
ASK 1996	14/174	2/166		7.06%	4.58[1.68,12.48]
Subtotal (95% CI)	**497**	**486**		**23.37%**	**6.03[3.47,10.47]**
Total events: 50 (Thrombolysis), 4 (Control)					
Heterogeneity: Tau²=0; Chi²=0.48, df=3(P=0.92); I²=0%					
Test for overall effect: Z=6.39(P<0.0001)					
1.2.3 Intravenous rt-PA versus control					
Haley 1993	0/14	1/13		0.46%	0.13[0,6.33]
NINDS 1995	9/312	1/312		4.56%	5.07[1.45,17.67]
ECASS 1995	19/313	7/307		11.53%	2.56[1.17,5.62]
ECASS II 1998	18/409	4/391		9.9%	3.53[1.51,8.24]
ATLANTIS B 1999	8/307	1/306		4.11%	4.82[1.29,17.96]
ATLANTIS A 2000	8/71	0/71		3.51%	8.2[1.98,33.99]
ECASS 3 2008	3/418	0/404		1.38%	7.18[0.74,69.24]
IST3 2012	55/1515	7/1520		28.08%	4.87[2.95,8.06]
Subtotal (95% CI)	**3359**	**3324**		**63.53%**	**4.18[2.99,5.84]**
Total events: 120 (Thrombolysis), 21 (Control)					
Heterogeneity: Tau²=0; Chi²=6.29, df=7(P=0.51); I²=0%					
Test for overall effect: Z=8.38(P<0.0001)					
1.2.4 Intravenous streptokinase plus oral aspirin versus oral aspirin					
MAST-I 1995	13/156	2/153		6.62%	4.56[1.62,12.84]
Subtotal (95% CI)	**156**	**153**		**6.62%**	**4.56[1.62,12.84]**
Total events: 13 (Thrombolysis), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.87(P=0)					

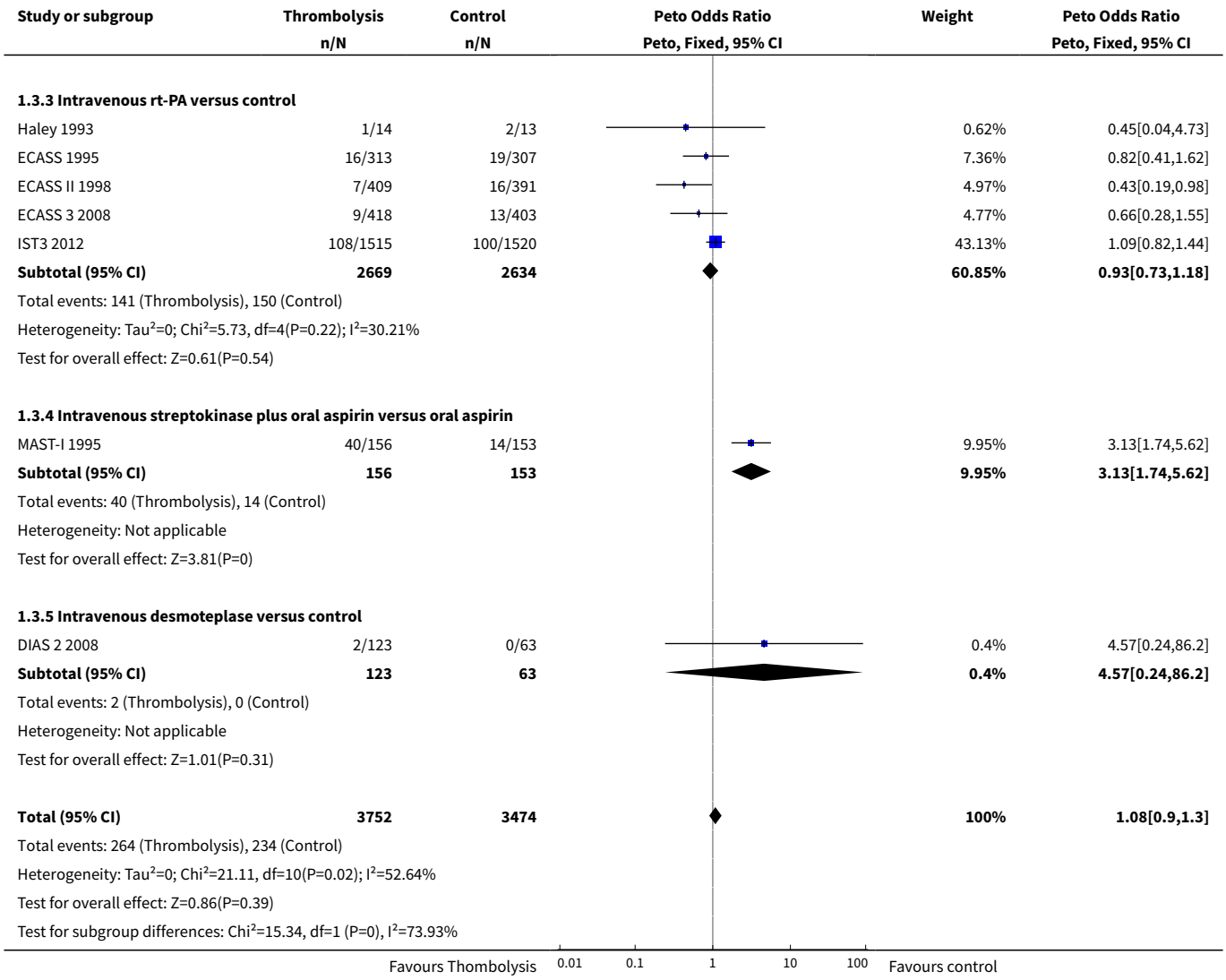


Favours Thombolysis — Favours control

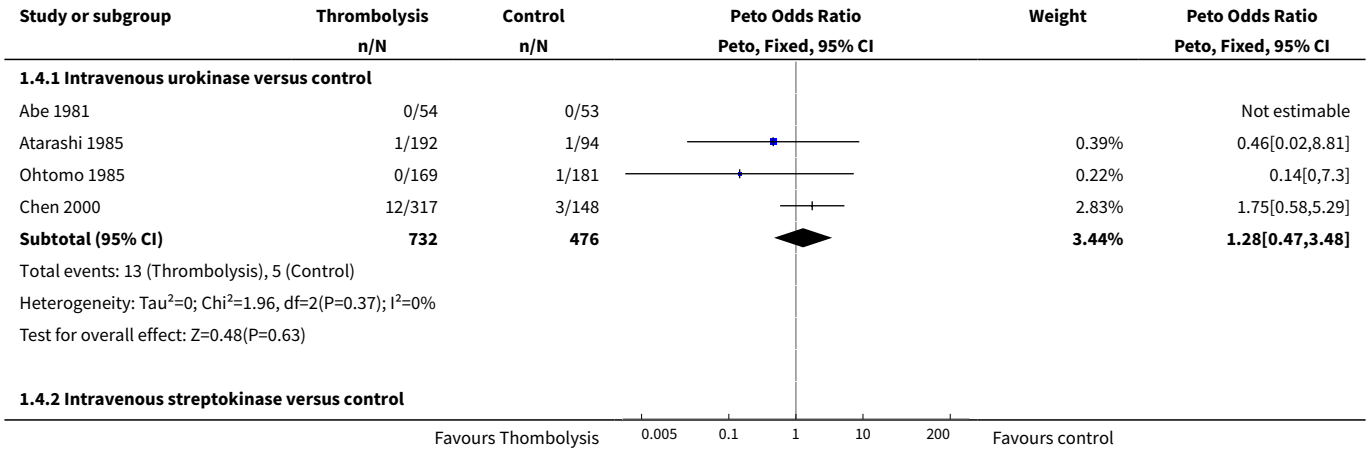


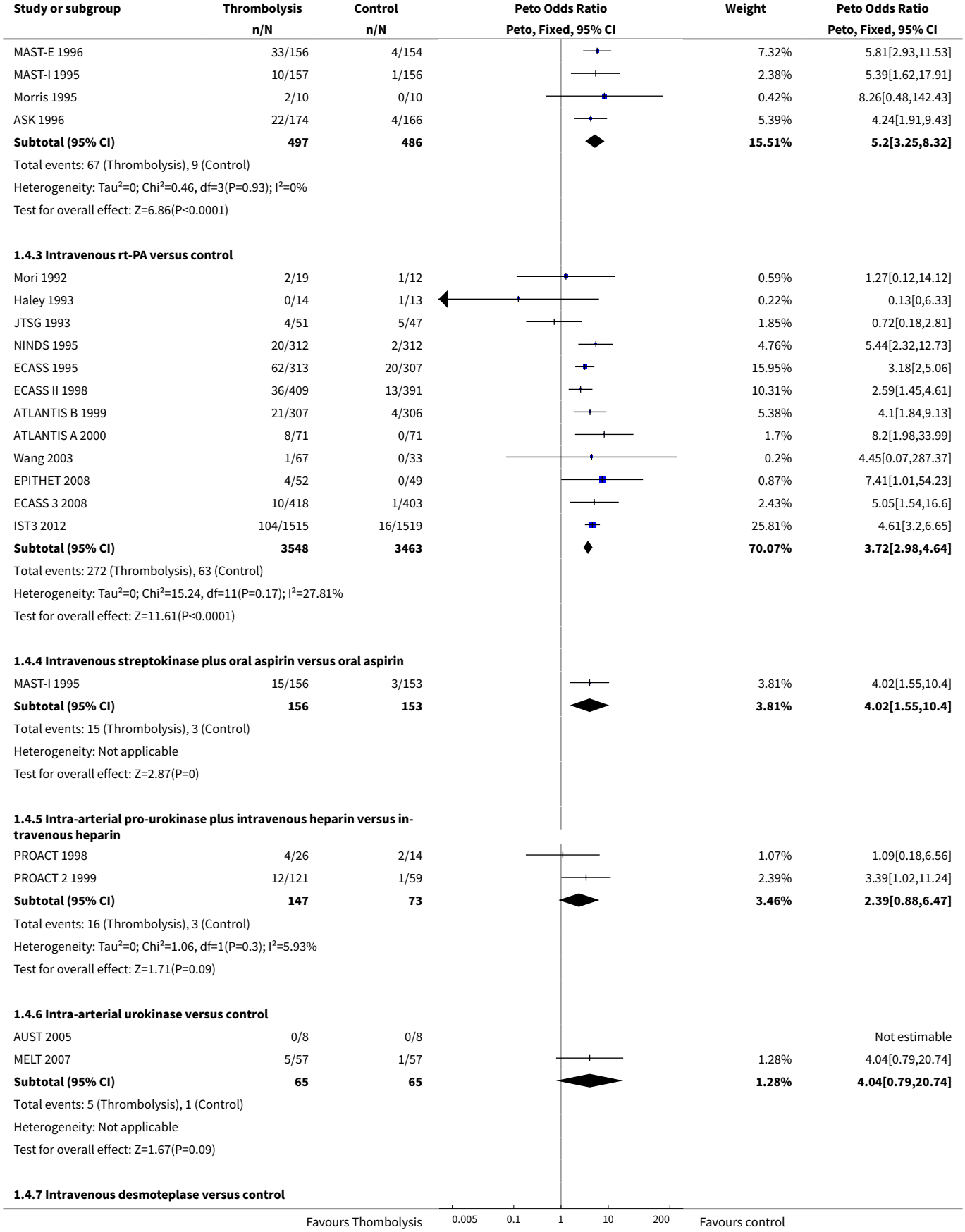
Analysis 1.3. Comparison 1 Any thrombolytic agent versus control, Outcome 3 Deaths within the first 7 to 10 days from causes other than fatal intracranial haemorrhage.



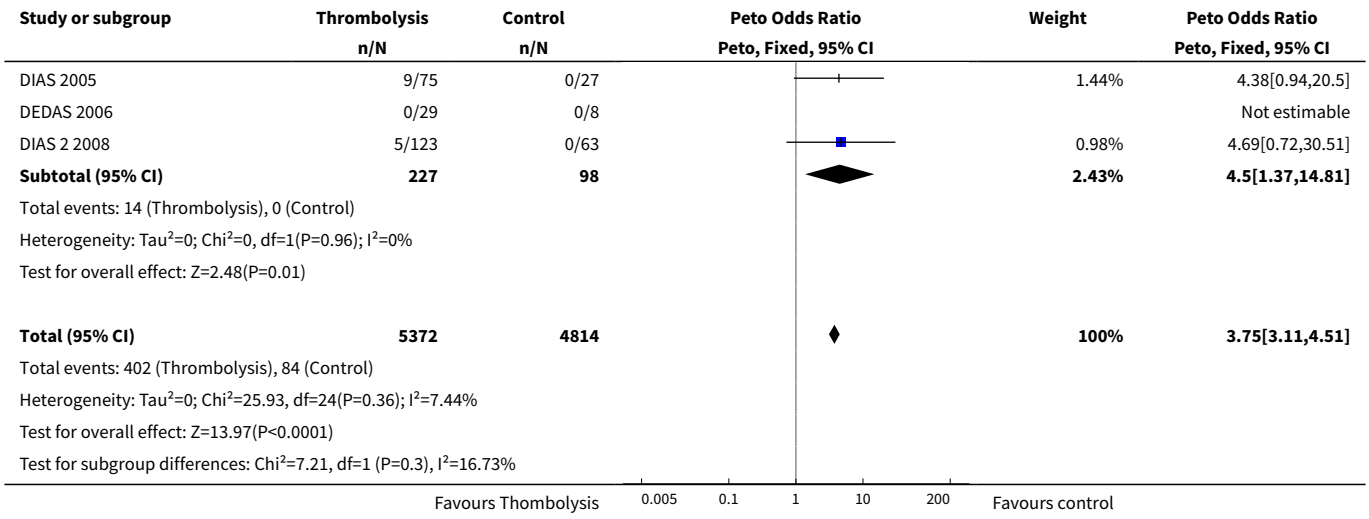


Analysis 1.4. Comparison 1 Any thrombolytic agent versus control, Outcome 4 Symptomatic (including fatal) intracranial haemorrhage within 7 to 10 days.

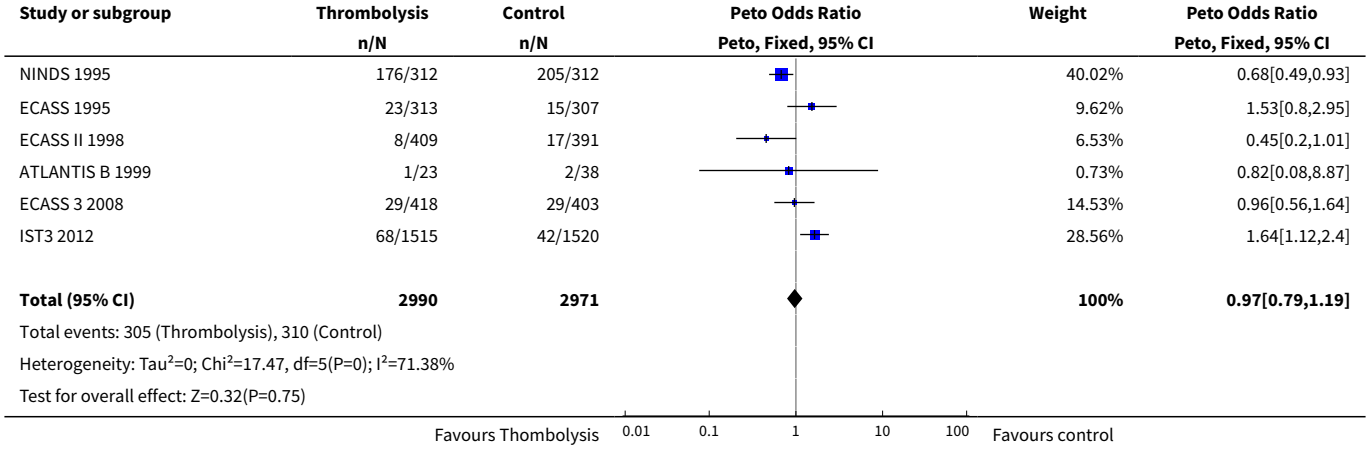




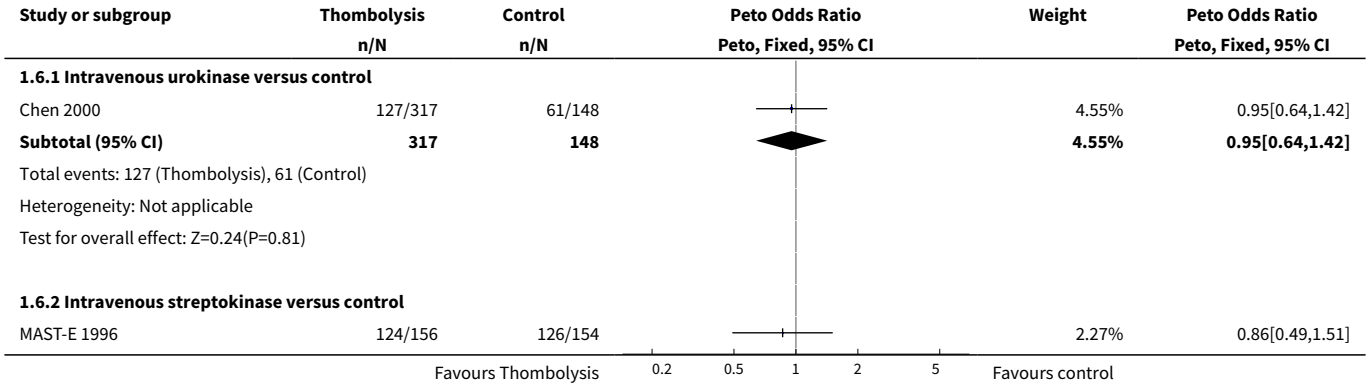
Study or subgroup	Thrombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
MAST-E 1996	33/156	4/154		7.32%	5.81[2.93,11.53]
MAST-I 1995	10/157	1/156		2.38%	5.39[1.62,17.91]
Morris 1995	2/10	0/10		0.42%	8.26[0.48,142.43]
ASK 1996	22/174	4/166		5.39%	4.24[1.91,9.43]
Subtotal (95% CI)	**497**	**486**		**15.51%**	**5.2[3.25,8.32]**
Total events: 67 (Thrombolysis), 9 (Control)					
Heterogeneity: Tau²=0; Chi²=0.46, df=3(P=0.93); I²=0%					
Test for overall effect: Z=6.86(P<0.0001)					
1.4.3 Intravenous rt-PA versus control					
Mori 1992	2/19	1/12		0.59%	1.27[0.12,14.12]
Haley 1993	0/14	1/13		0.22%	0.13[0,6.33]
JTSG 1993	4/51	5/47		1.85%	0.72[0.18,2.81]
NINDS 1995	20/312	2/312		4.76%	5.44[2.32,12.73]
ECASS 1995	62/313	20/307		15.95%	3.18[2,5.06]
ECASS II 1998	36/409	13/391		10.31%	2.59[1.45,4.61]
ATLANTIS B 1999	21/307	4/306		5.38%	4.1[1.84,9.13]
ATLANTIS A 2000	8/71	0/71		1.7%	8.2[1.98,33.99]
Wang 2003	1/67	0/33		0.2%	4.45[0.07,287.37]
EPITHET 2008	4/52	0/49		0.87%	7.41[1.01,54.23]
ECASS 3 2008	10/418	1/403		2.43%	5.05[1.54,16.6]
IST3 2012	104/1515	16/1519		25.81%	4.61[3.2,6.65]
Subtotal (95% CI)	**3548**	**3463**		**70.07%**	**3.72[2.98,4.64]**
Total events: 272 (Thrombolysis), 63 (Control)					
Heterogeneity: Tau²=0; Chi²=15.24, df=11(P=0.17); I²=27.81%					
Test for overall effect: Z=11.61(P<0.0001)					
1.4.4 Intravenous streptokinase plus oral aspirin versus oral aspirin					
MAST-I 1995	15/156	3/153		3.81%	4.02[1.55,10.4]
Subtotal (95% CI)	**156**	**153**		**3.81%**	**4.02[1.55,10.4]**
Total events: 15 (Thrombolysis), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.87(P=0)					
1.4.5 Intra-arterial pro-urokinase plus intravenous heparin versus intravenous heparin					
PROACT 1998	4/26	2/14		1.07%	1.09[0.18,6.56]
PROACT 2 1999	12/121	1/59		2.39%	3.39[1.02,11.24]
Subtotal (95% CI)	**147**	**73**		**3.46%**	**2.39[0.88,6.47]**
Total events: 16 (Thrombolysis), 3 (Control)					
Heterogeneity: Tau²=0; Chi²=1.06, df=1(P=0.3); I²=5.93%					
Test for overall effect: Z=1.71(P=0.09)					
1.4.6 Intra-arterial urokinase versus control					
AUST 2005	0/8	0/8			Not estimable
MELT 2007	5/57	1/57		1.28%	4.04[0.79,20.74]
Subtotal (95% CI)	**65**	**65**		**1.28%**	**4.04[0.79,20.74]**
Total events: 5 (Thrombolysis), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.67(P=0.09)					
1.4.7 Intravenous desmoteplase versus control					

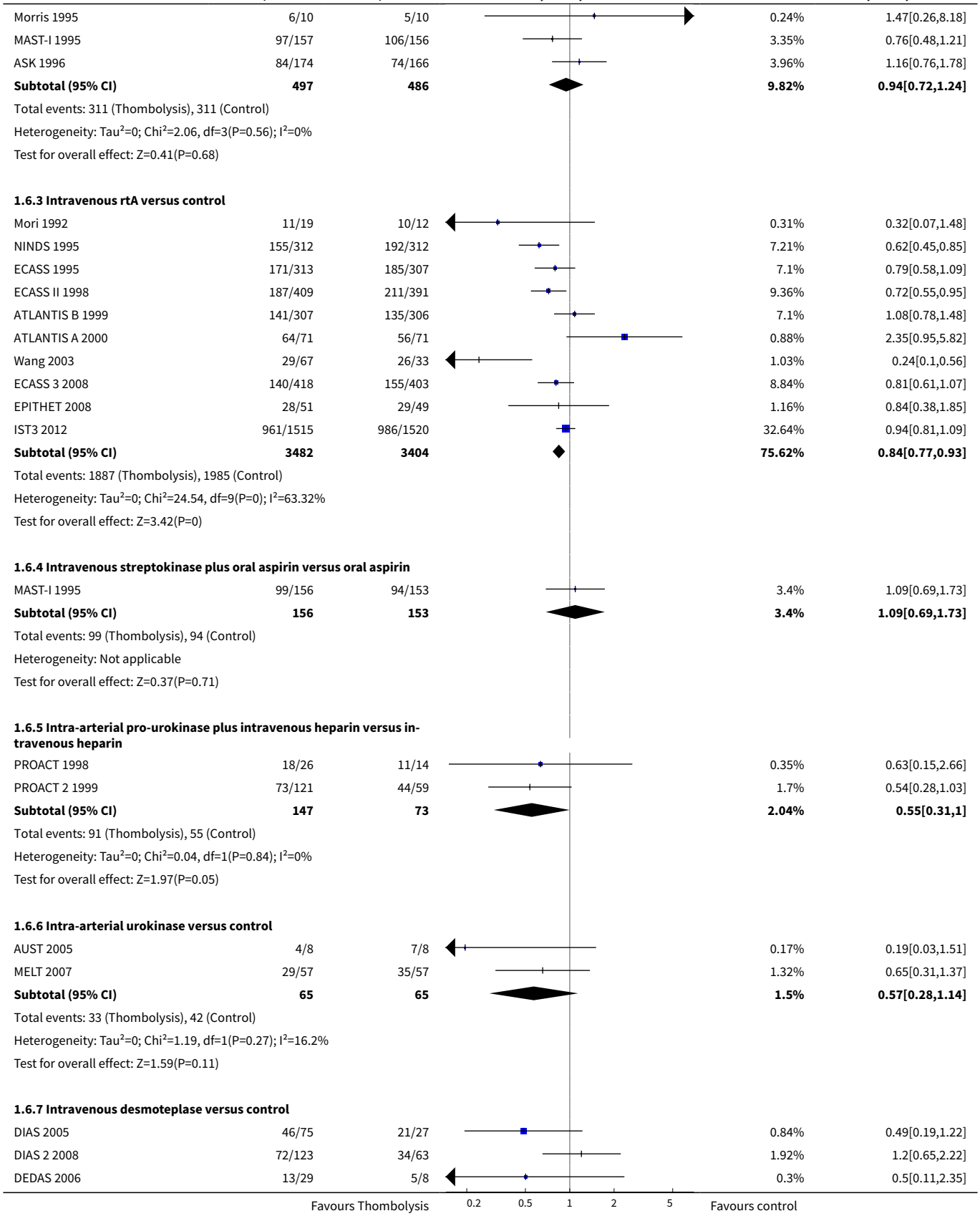


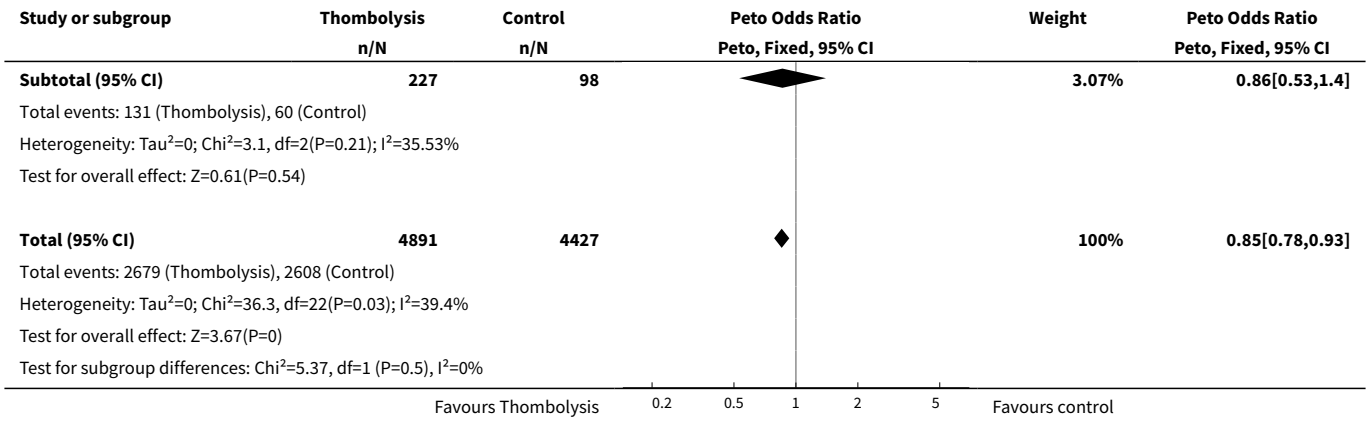
Analysis 1.5. Comparison 1 Any thrombolytic agent versus control, Outcome 5 Symptomatic (including fatal) cerebral oedema.



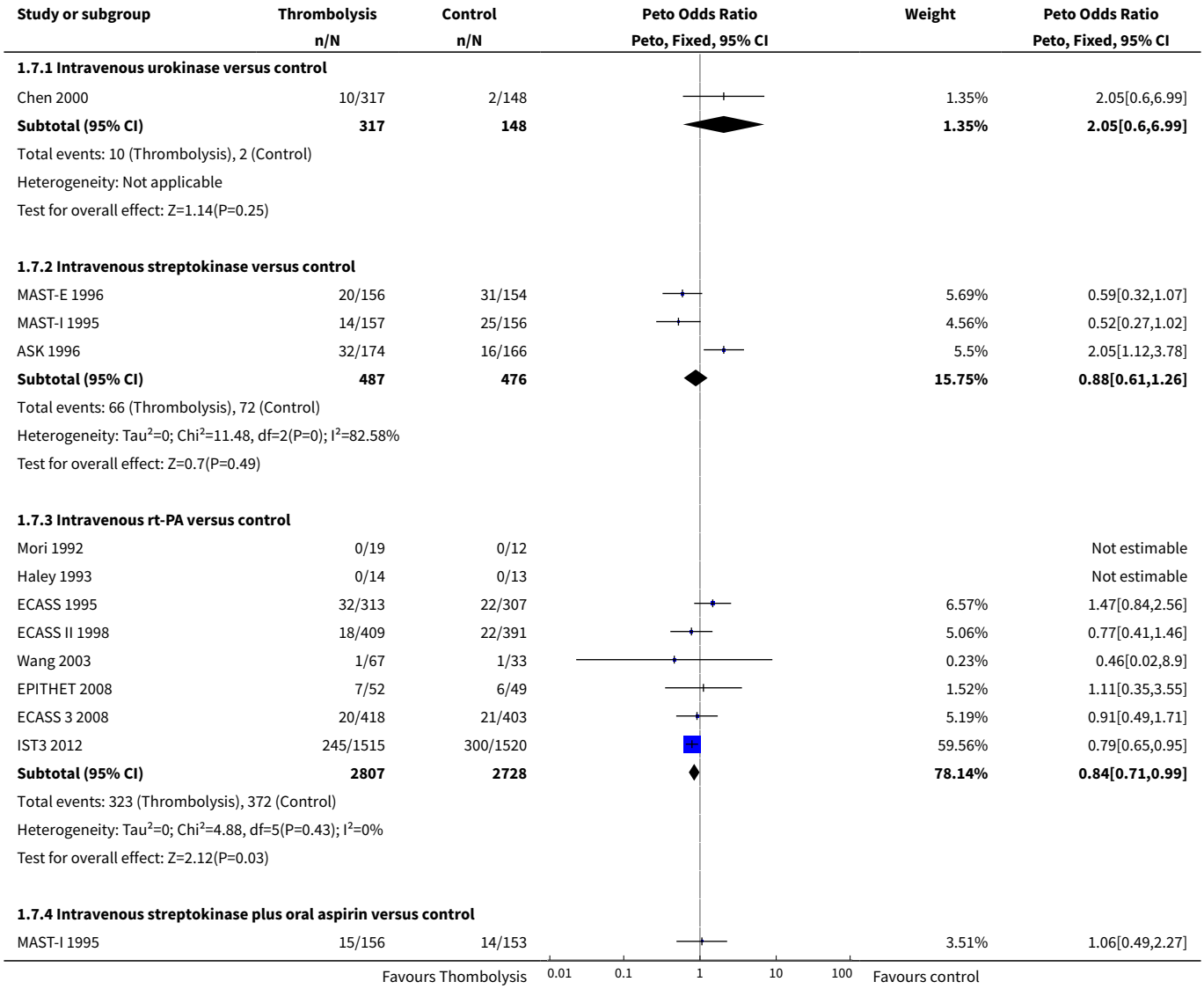
Analysis 1.6. Comparison 1 Any thrombolytic agent versus control, Outcome 6 Death or dependency at the end of follow-up.

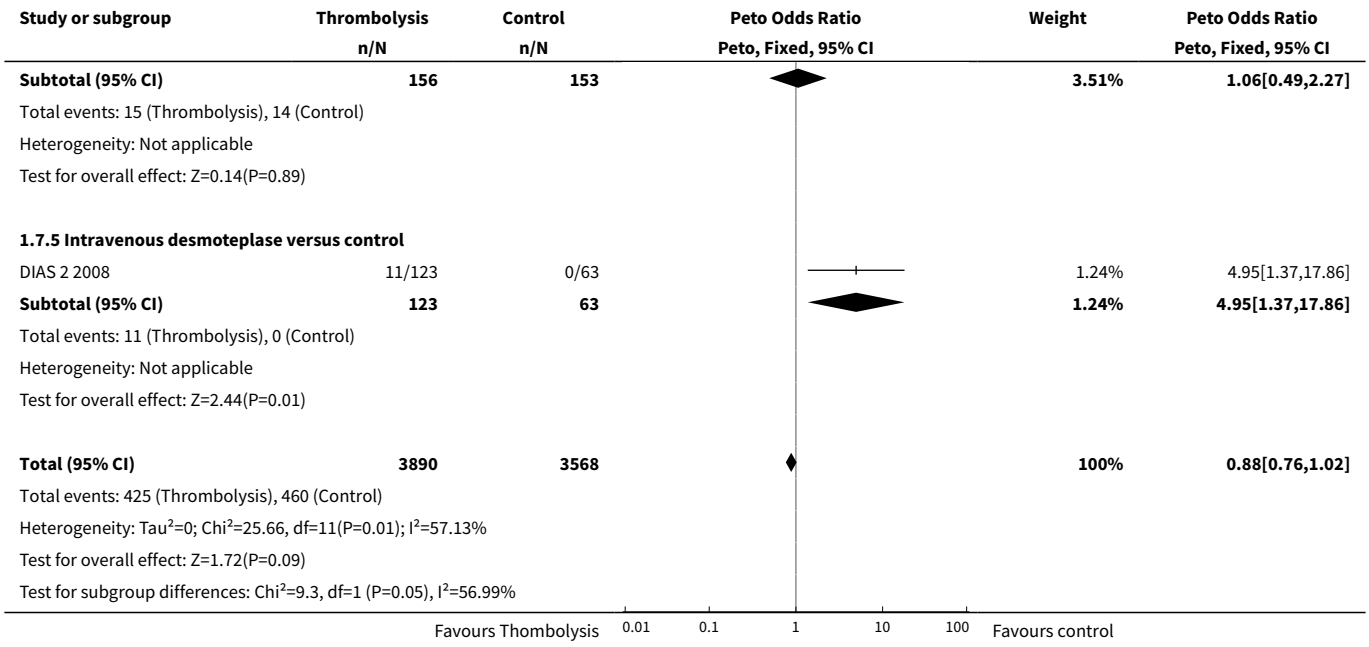




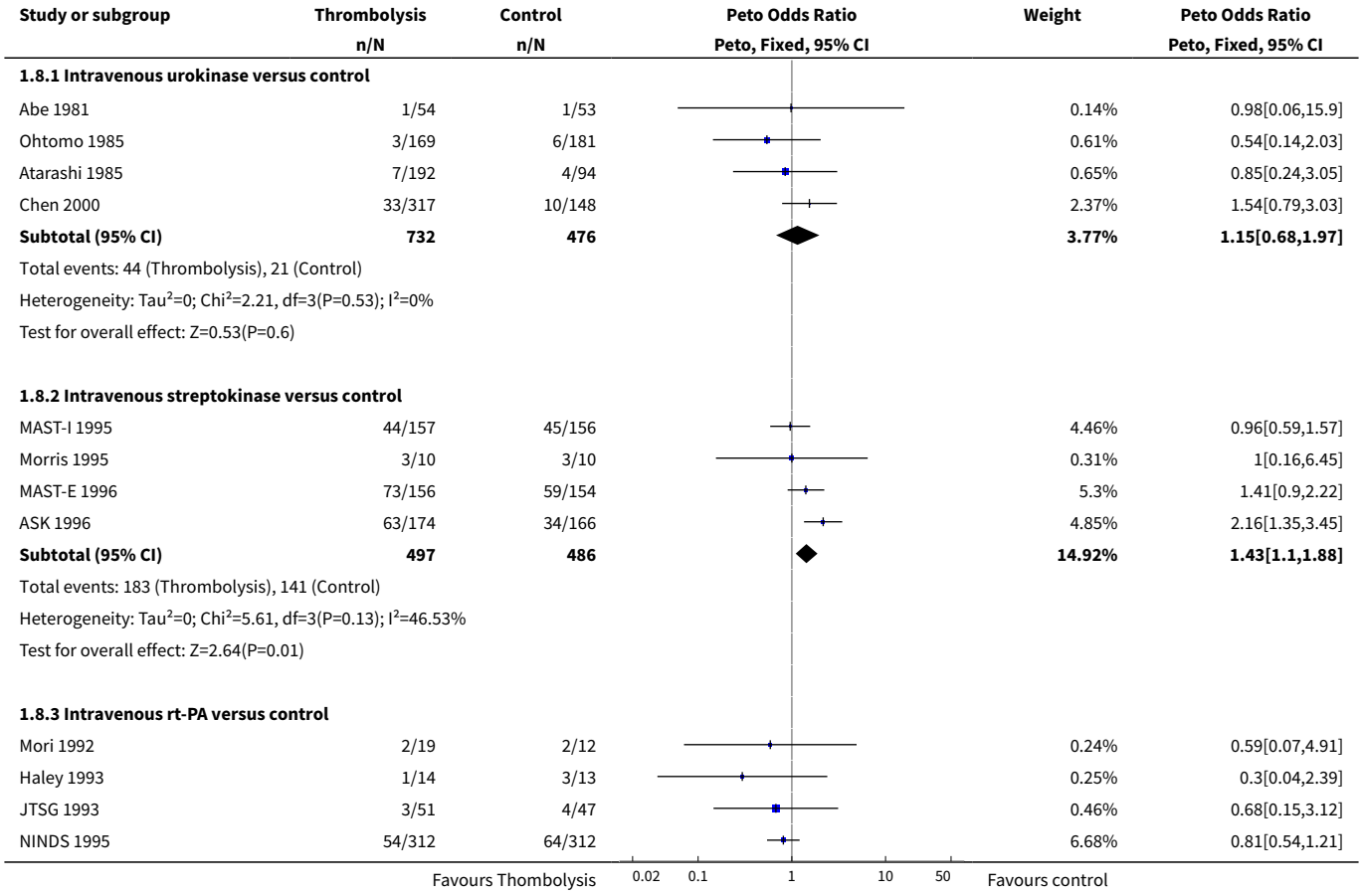


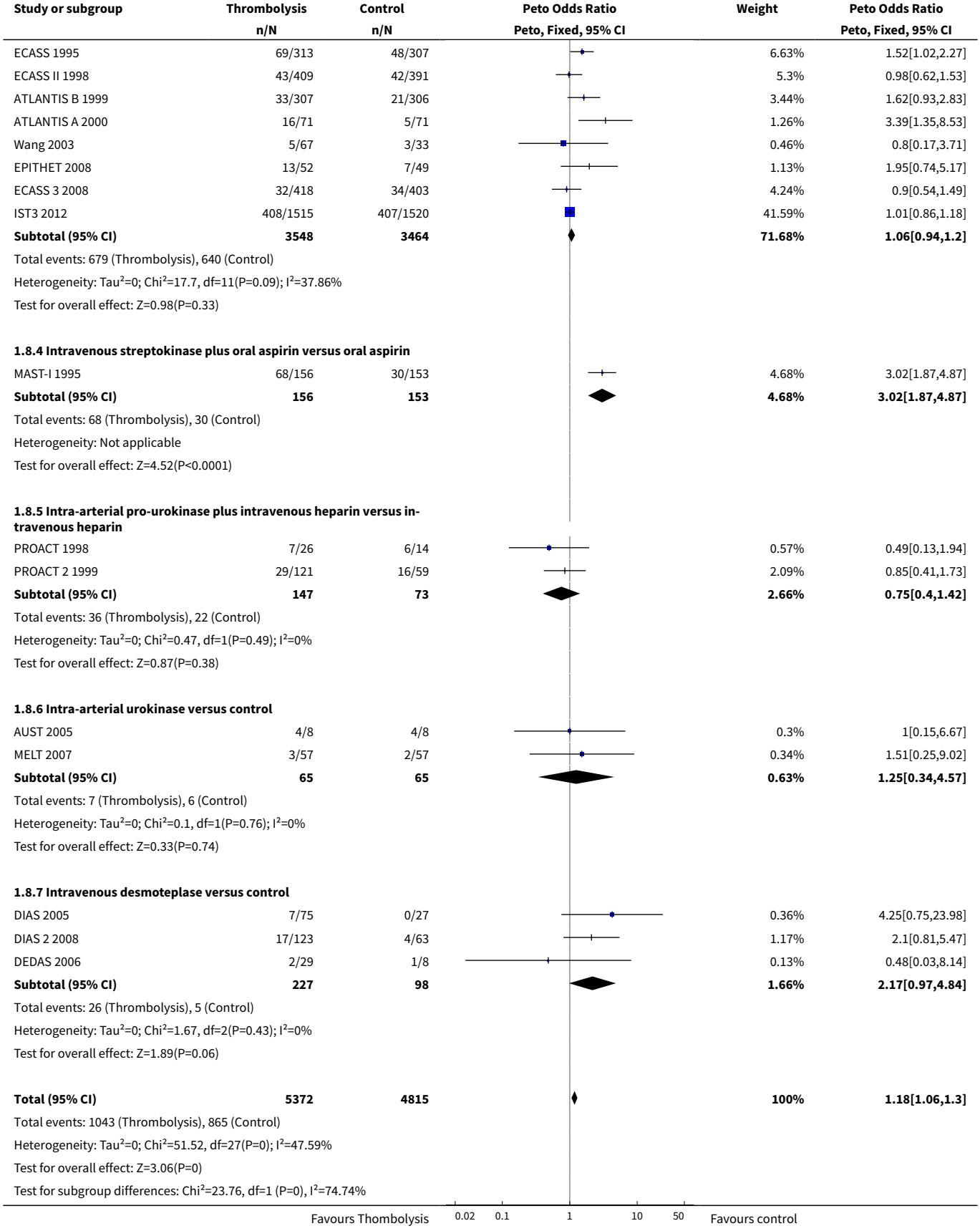
Analysis 1.7. Comparison 1 Any thrombolytic agent versus control, Outcome 7 Deaths occurring between 7 and 10 days and the end of follow-up.





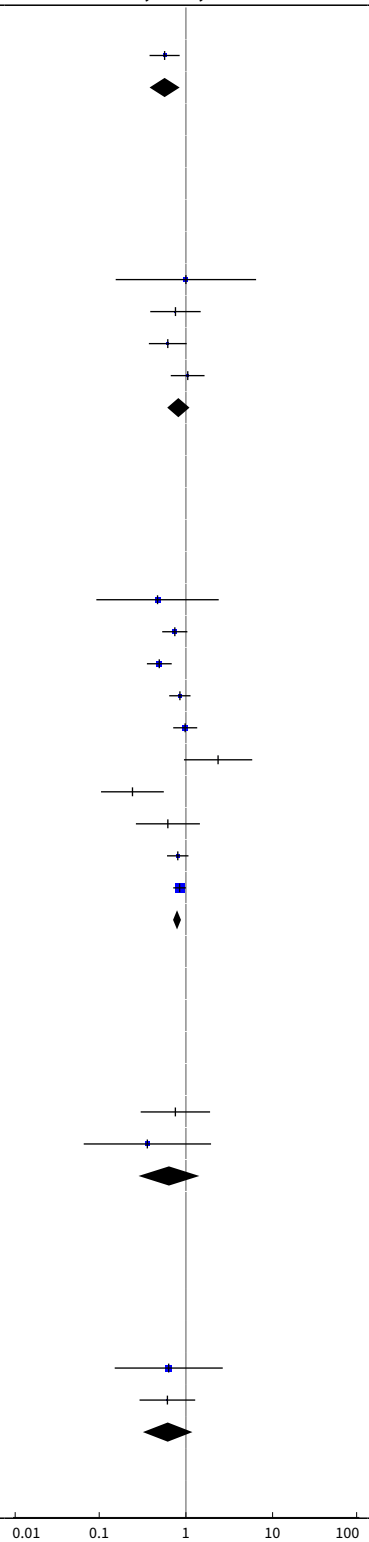
Analysis 1.8. Comparison 1 Any thrombolytic agent versus control, Outcome 8 Deaths from all causes during follow-up.

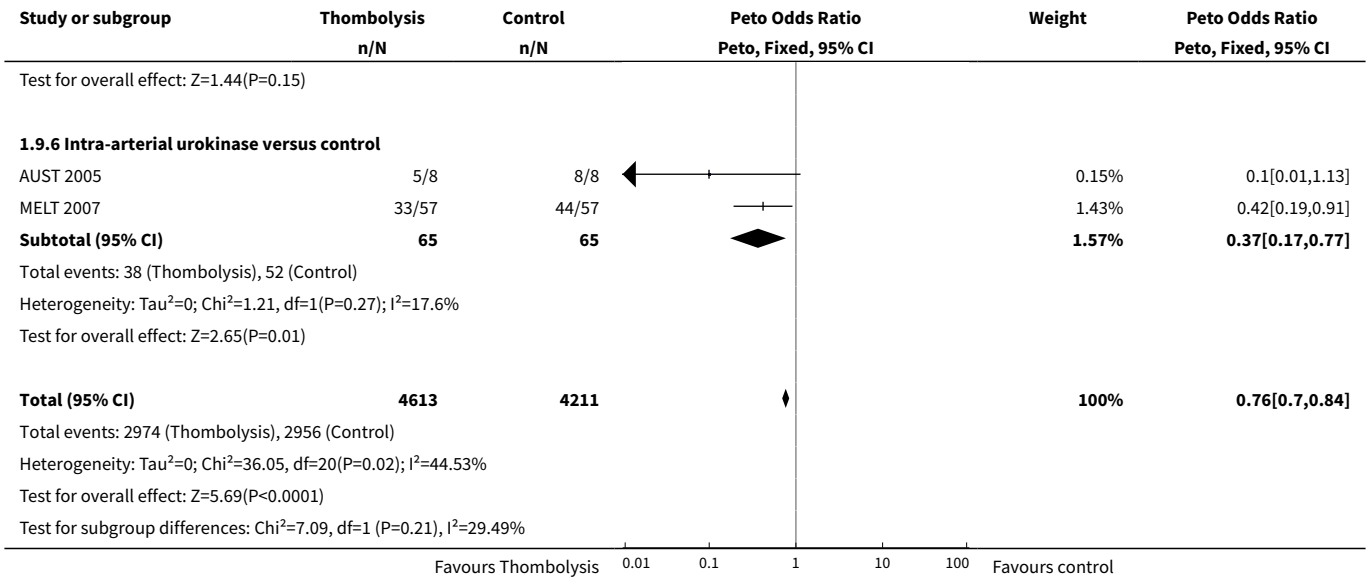




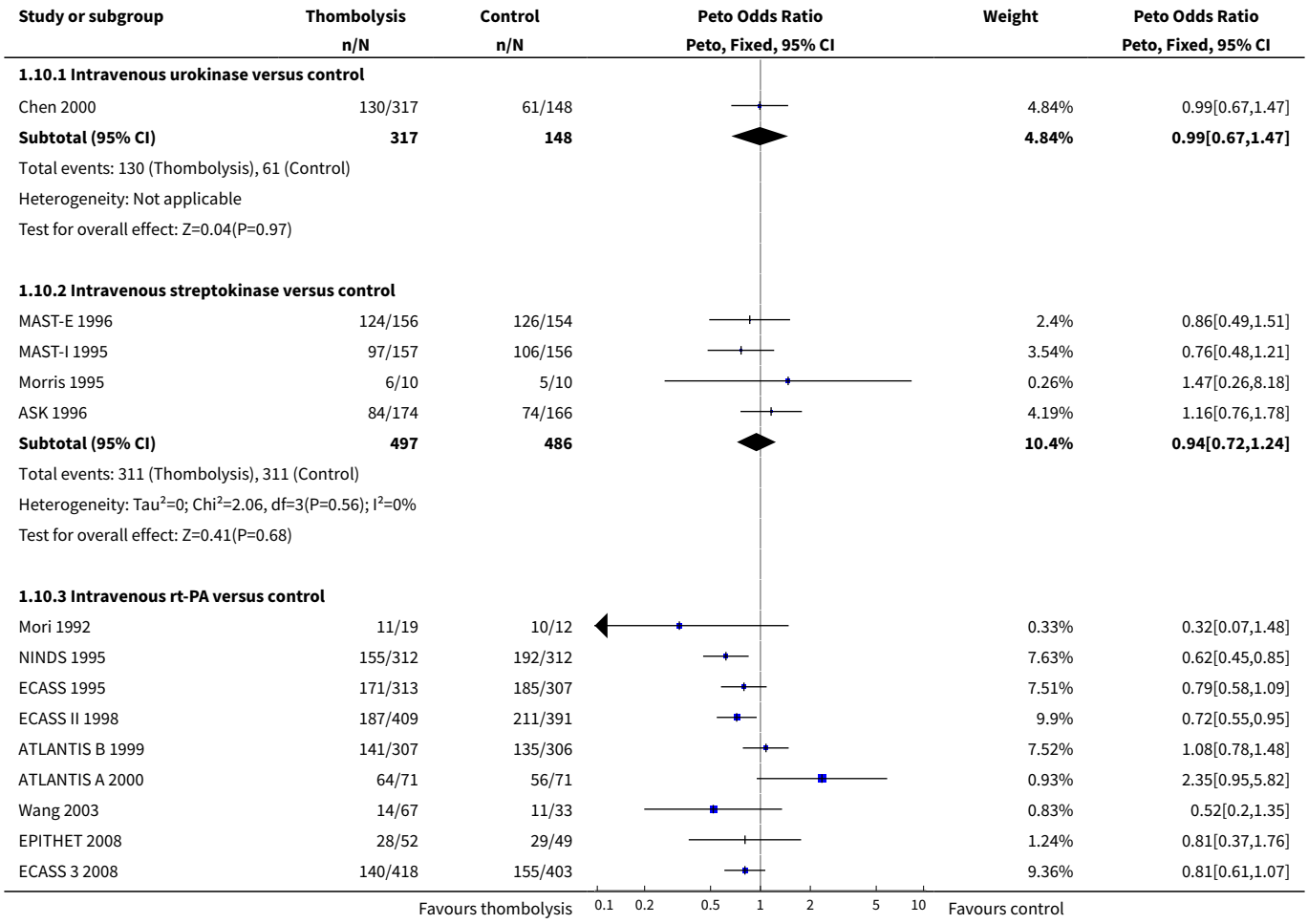
Analysis 1.9. Comparison 1 Any thrombolytic agent versus control, Outcome 9 Death or dependency defined as mRS 2 to 6.

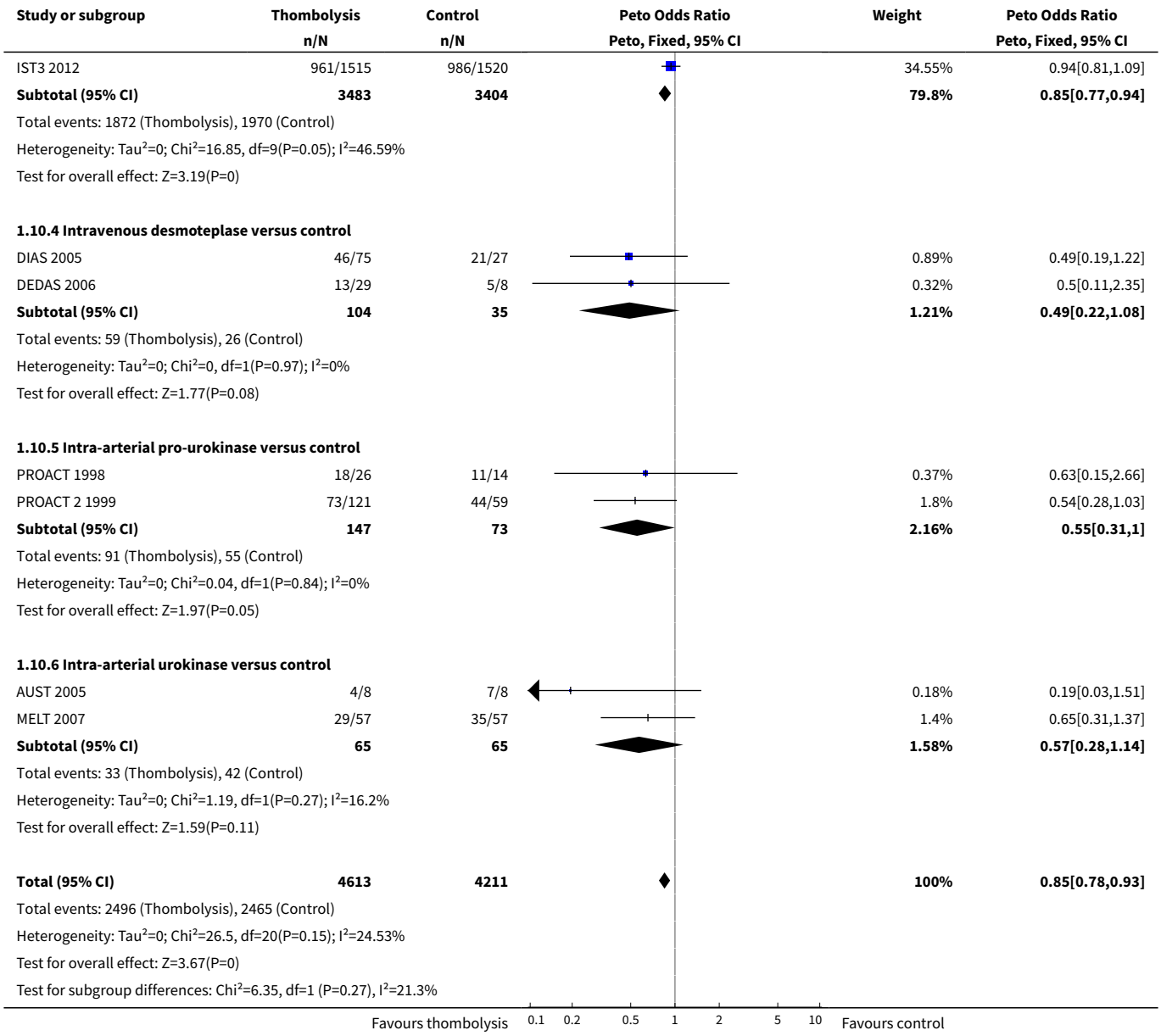
Study or subgroup	Thombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.9.1 Intravenous urokinase versus control					
Chen 2000	180/317	104/148		5.44%	0.57[0.38,0.85]
Subtotal (95% CI)	**317**	**148**		**5.44%**	**0.57[0.38,0.85]**
Total events: 180 (Thombolysis), 104 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.78(P=0.01)					
1.9.2 Intravenous streptokinase versus control					
Morris 1995	7/10	7/10		0.25%	1[0.16,6.45]
MAST-E 1996	134/156	137/154		1.94%	0.76[0.39,1.48]
MAST-I 1995	108/157	122/156		3.46%	0.62[0.37,1.02]
ASK 1996	115/174	108/166		4.35%	1.05[0.67,1.64]
Subtotal (95% CI)	**497**	**486**		**10%**	**0.82[0.61,1.1]**
Total events: 364 (Thombolysis), 374 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.47, df=3(P=0.48); I^2=0%					
Test for overall effect: Z=1.33(P=0.18)					
1.9.3 Intravenous rt-PA versus control					
Mori 1992	13/19	10/12		0.33%	0.47[0.09,2.39]
ECASS 1995	201/313	217/307		7.72%	0.75[0.53,1.04]
NINDS 1995	179/312	229/312		8.01%	0.49[0.35,0.69]
ECASS II 1998	244/409	248/391		10.73%	0.85[0.64,1.13]
ATLANTIS B 1999	161/307	162/306		8.66%	0.98[0.71,1.35]
ATLANTIS A 2000	64/71	56/71		1.06%	2.35[0.95,5.82]
Wang 2003	29/67	26/33		1.25%	0.24[0.1,0.56]
EPITHET 2008	34/52	37/49		1.2%	0.62[0.26,1.45]
ECASS 3 2008	140/418	155/403		10.71%	0.81[0.61,1.07]
IST3 2012	1152/1515	1200/1520		29.97%	0.85[0.71,1]
Subtotal (95% CI)	**3483**	**3404**		**79.64%**	**0.79[0.71,0.88]**
Total events: 2217 (Thombolysis), 2340 (Control)					
Heterogeneity: Tau^2=0; Chi^2=24.71, df=9(P=0); I^2=63.57%					
Test for overall effect: Z=4.43(P<0.0001)					
1.9.4 Intravenous desmoteplase versus control					
DIAS 2005	48/75	19/27		1.02%	0.76[0.3,1.9]
DEDAS 2006	19/29	7/8		0.3%	0.36[0.07,1.95]
Subtotal (95% CI)	**104**	**35**		**1.33%**	**0.64[0.28,1.43]**
Total events: 67 (Thombolysis), 26 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.57, df=1(P=0.45); I^2=0%					
Test for overall effect: Z=1.09(P=0.28)					
1.9.5 Intra-arterial pro-urokinase versus control					
PROACT 1998	18/26	11/14		0.42%	0.63[0.15,2.66]
PROACT 2 1999	90/121	49/59		1.59%	0.61[0.29,1.28]
Subtotal (95% CI)	**147**	**73**		**2.01%**	**0.62[0.32,1.19]**
Total events: 108 (Thombolysis), 60 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%					



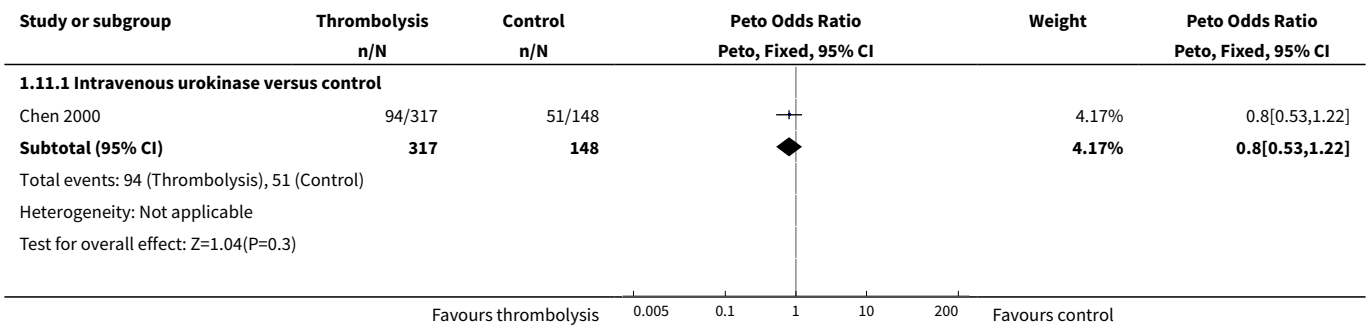


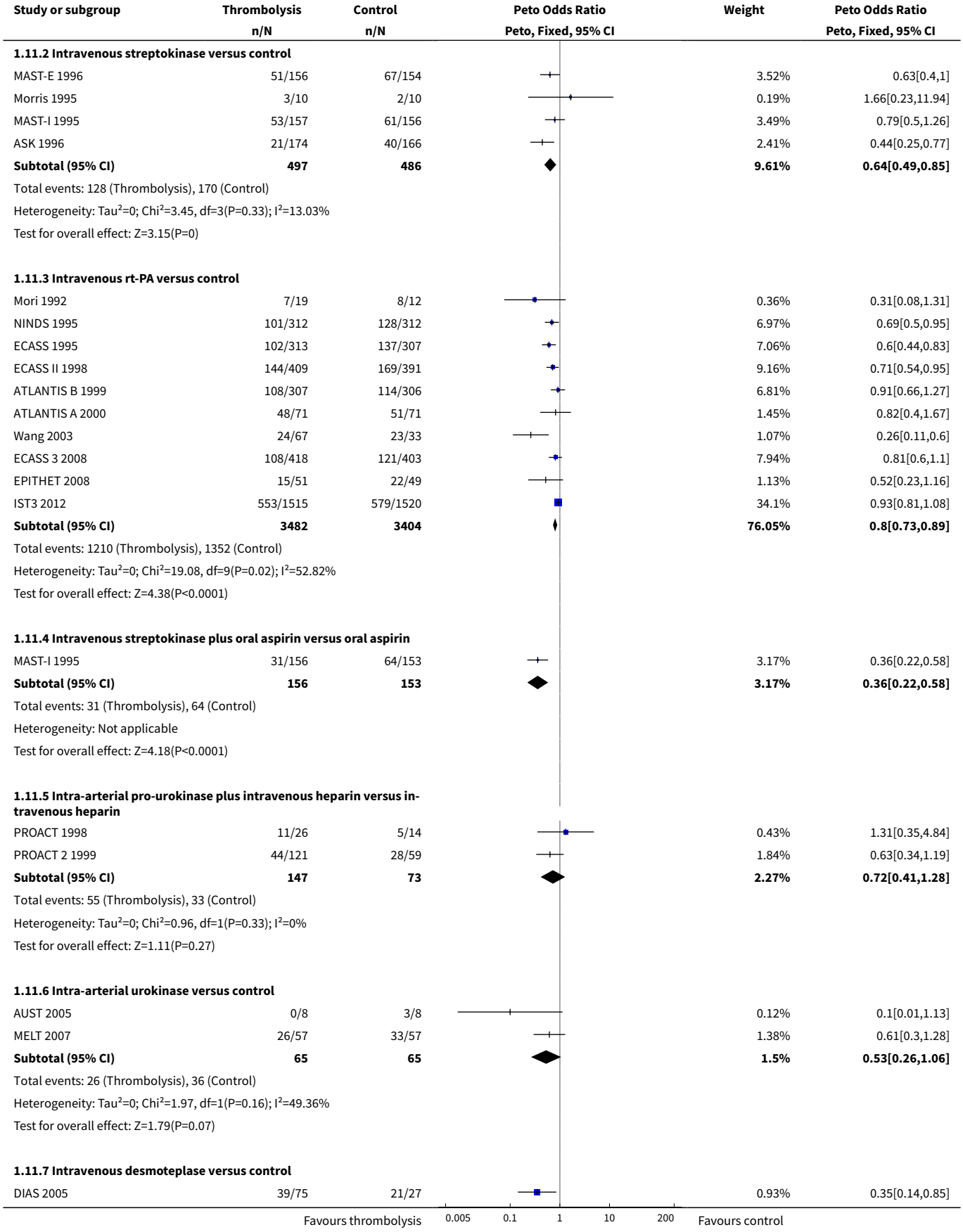
Analysis 1.10. Comparison 1 Any thrombolytic agent versus control, Outcome 10 Death or dependency defined as mRS 3 to 6.

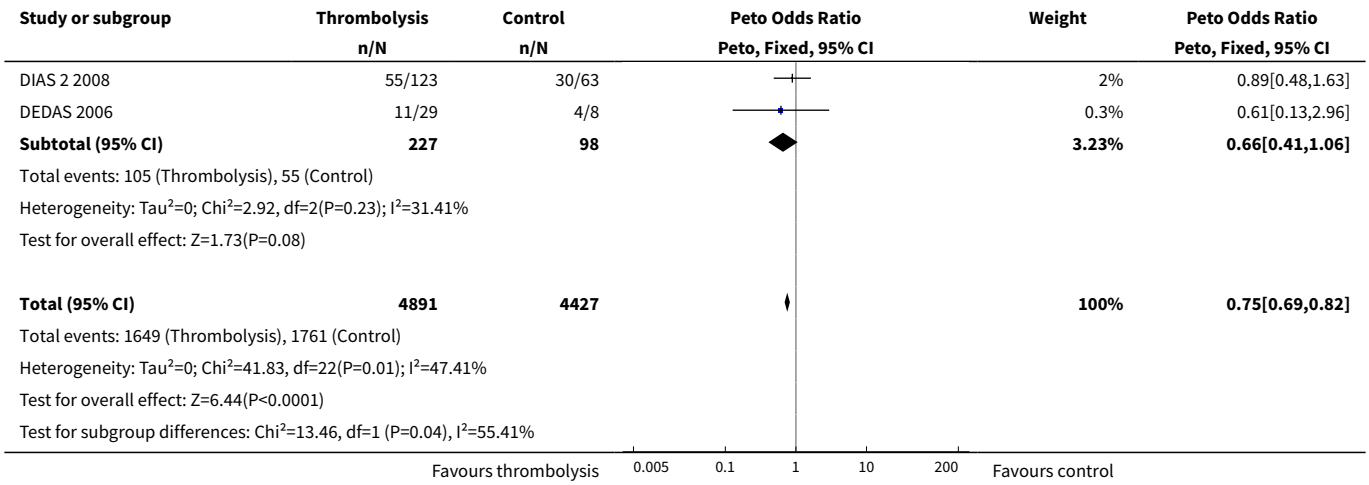




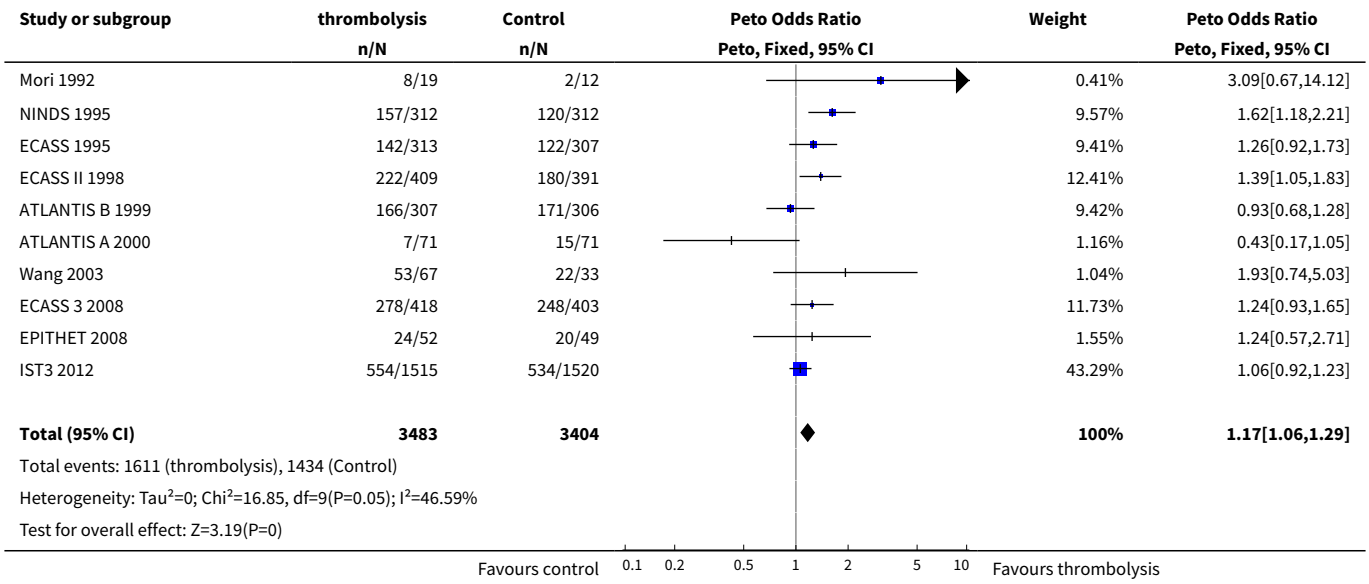
Analysis 1.11. Comparison 1 Any thrombolytic agent versus control, Outcome 11 Dependency at the end of follow-up defined as mRS 3 to 5.



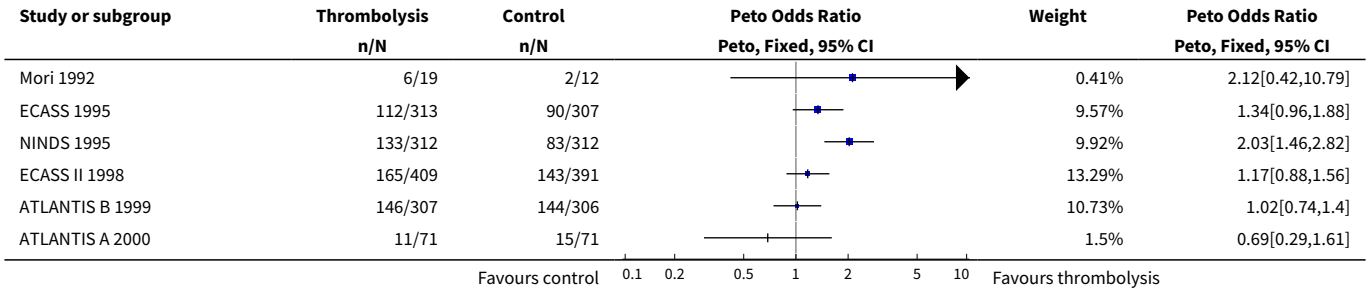


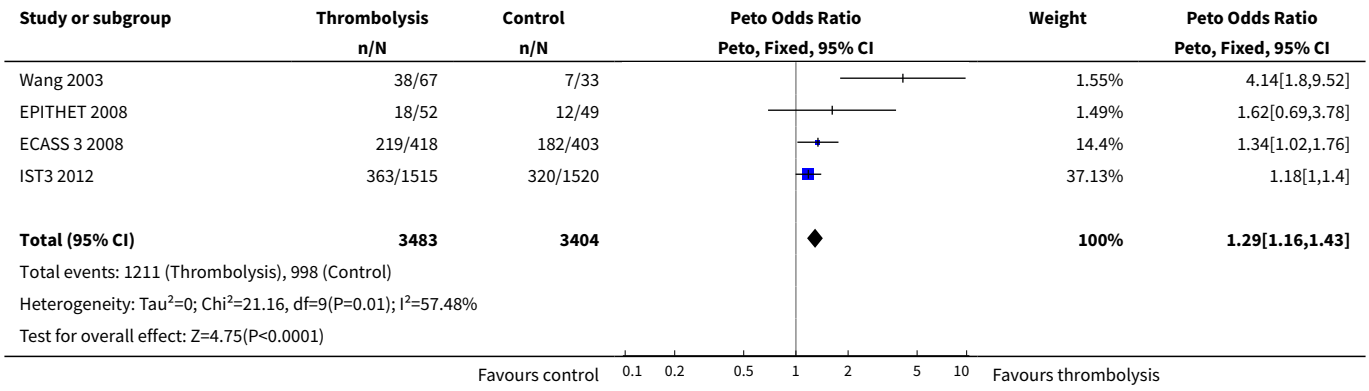


Analysis 1.12. Comparison 1 Any thrombolytic agent versus control, Outcome 12 Alive and independent (mRS 0 to 2) at end of follow-up, participants treated up to six hours.

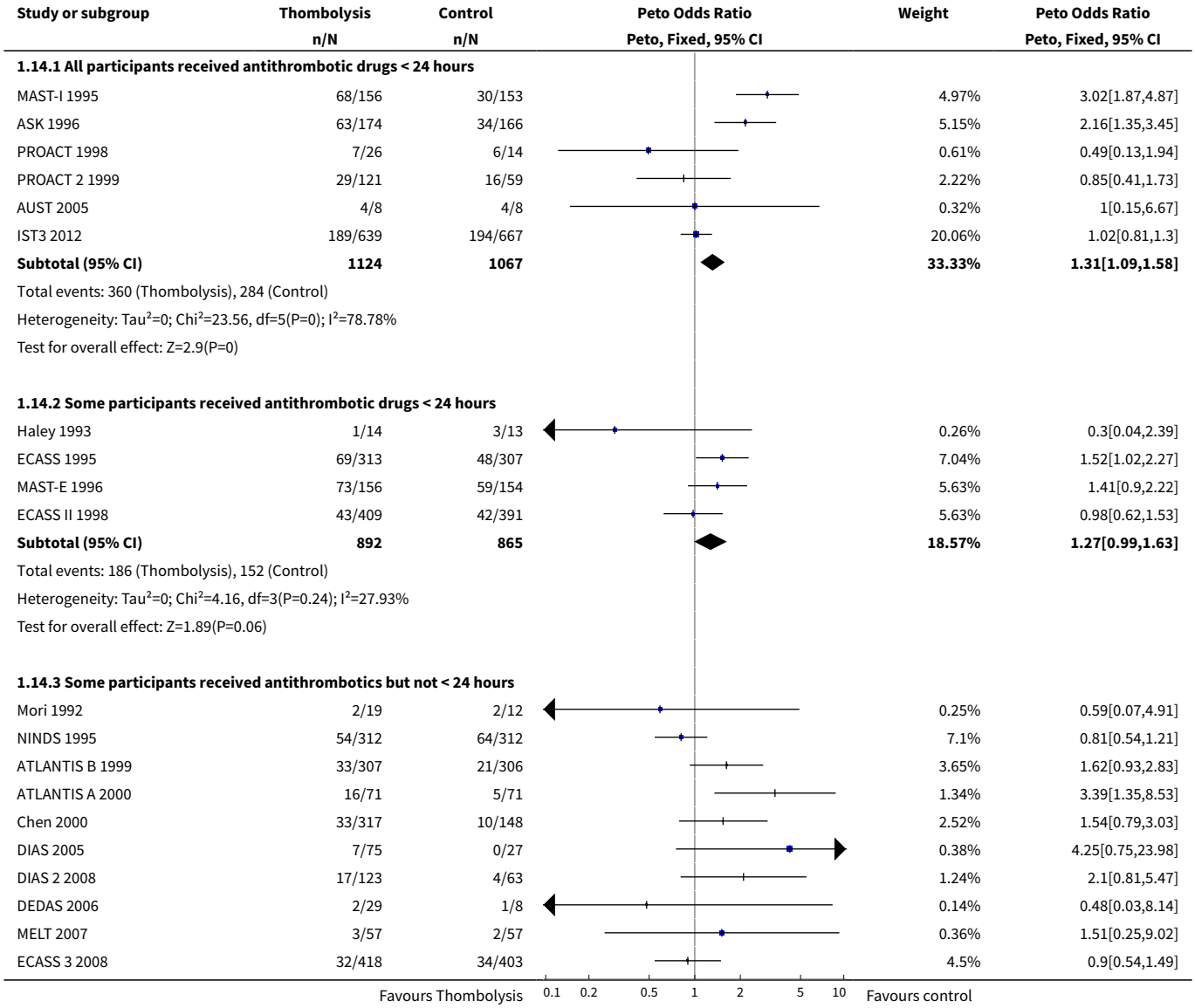


Analysis 1.13. Comparison 1 Any thrombolytic agent versus control, Outcome 13 Alive and favourable outcome (mRS 0 to 1) at end of follow-up, participants treated up to six hours.

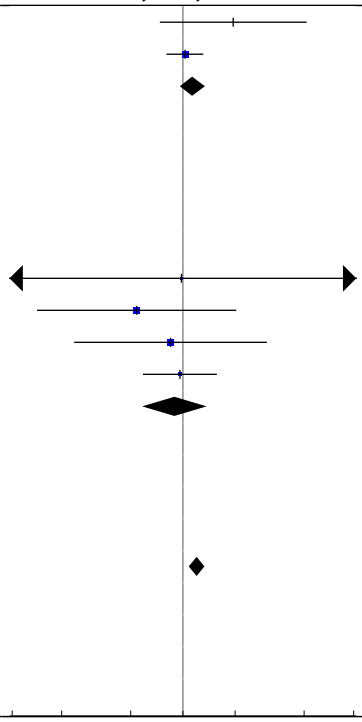




Analysis 1.14. Comparison 1 Any thrombolytic agent versus control, Outcome 14 Deaths from all causes ordered by antithrombotic drug use.

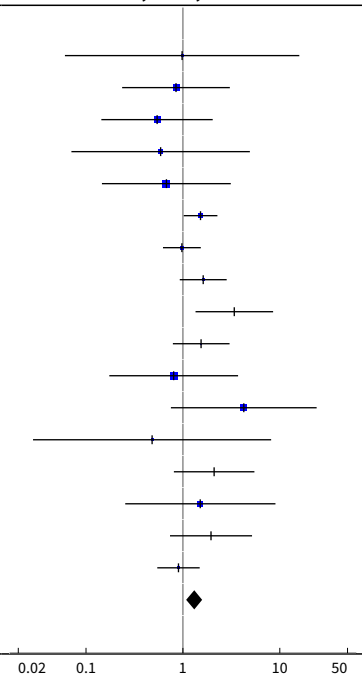


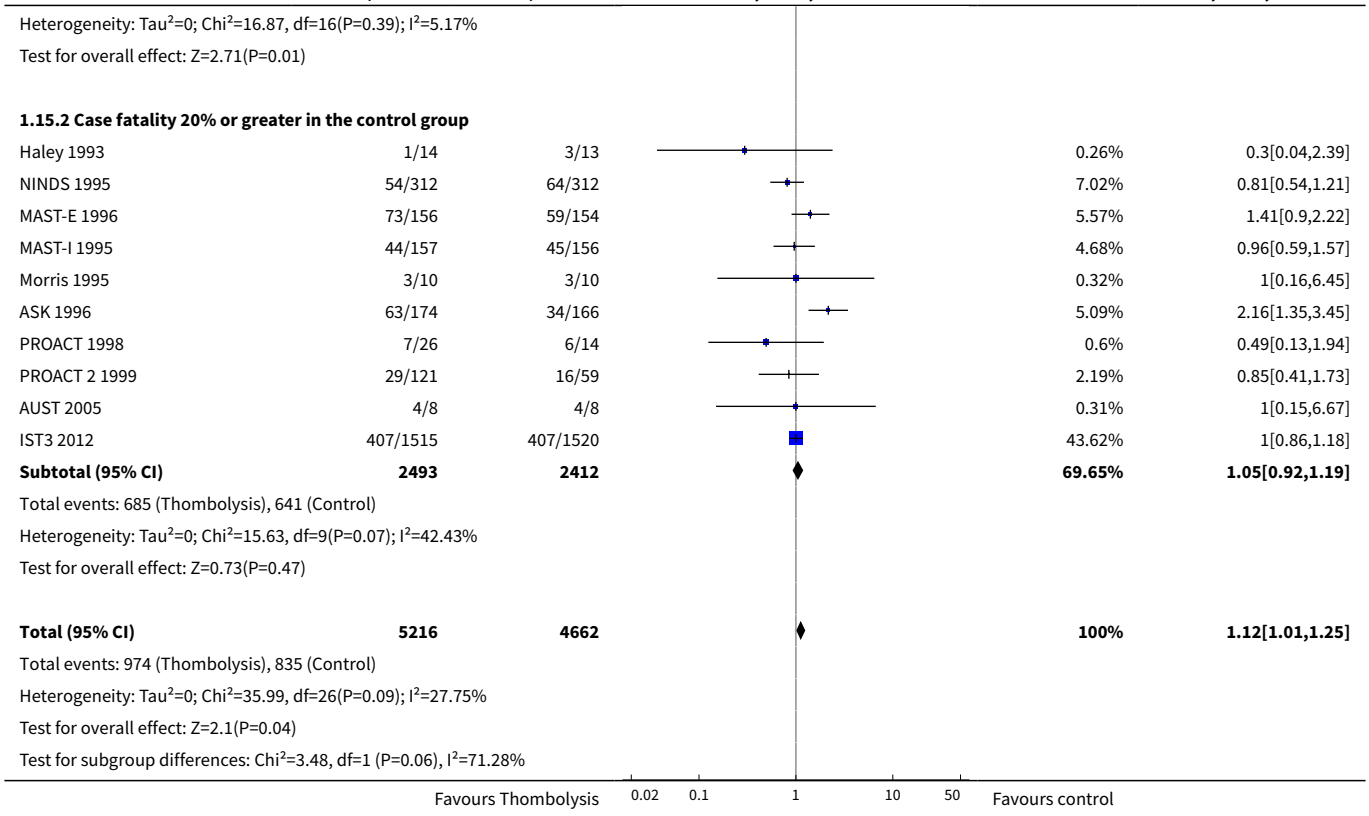
Study or subgroup	Thombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
EPITHET 2008	13/52	7/49		1.2%	1.95[0.74,5.17]
IST3 2012	174/729	165/705		19.19%	1.03[0.8,1.31]
Subtotal (95% CI)	**2509**	**2161**		**41.87%**	**1.13[0.96,1.34]**
Total events: 386 (Thombolysis), 315 (Control)					
Heterogeneity: Tau^2=0; Chi^2=17.76, df=11(P=0.09); I^2=38.07%					
Test for overall effect: Z=1.48(P=0.14)					
1.14.4 No participants received antithrombotic drugs < 10 days					
Abe 1981	1/54	1/53		0.15%	0.98[0.06,15.9]
Ohtomo 1985	3/169	6/181		0.65%	0.54[0.14,2.03]
Atarashi 1985	7/192	4/94		0.69%	0.85[0.24,3.05]
MAST-I 1995	44/157	45/156		4.73%	0.96[0.59,1.57]
Subtotal (95% CI)	**572**	**484**		**6.23%**	**0.89[0.58,1.37]**
Total events: 55 (Thombolysis), 56 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.64, df=3(P=0.89); I^2=0%					
Test for overall effect: Z=0.52(P=0.6)					
Total (95% CI)	**5097**	**4577**		**100%**	**1.2[1.08,1.33]**
Total events: 987 (Thombolysis), 807 (Control)					
Heterogeneity: Tau^2=0; Chi^2=49.58, df=25(P=0); I^2=49.58%					
Test for overall effect: Z=3.32(P=0)					
Test for subgroup differences: Chi^2=3.45, df=1 (P=0.33), I^2=13.13%					



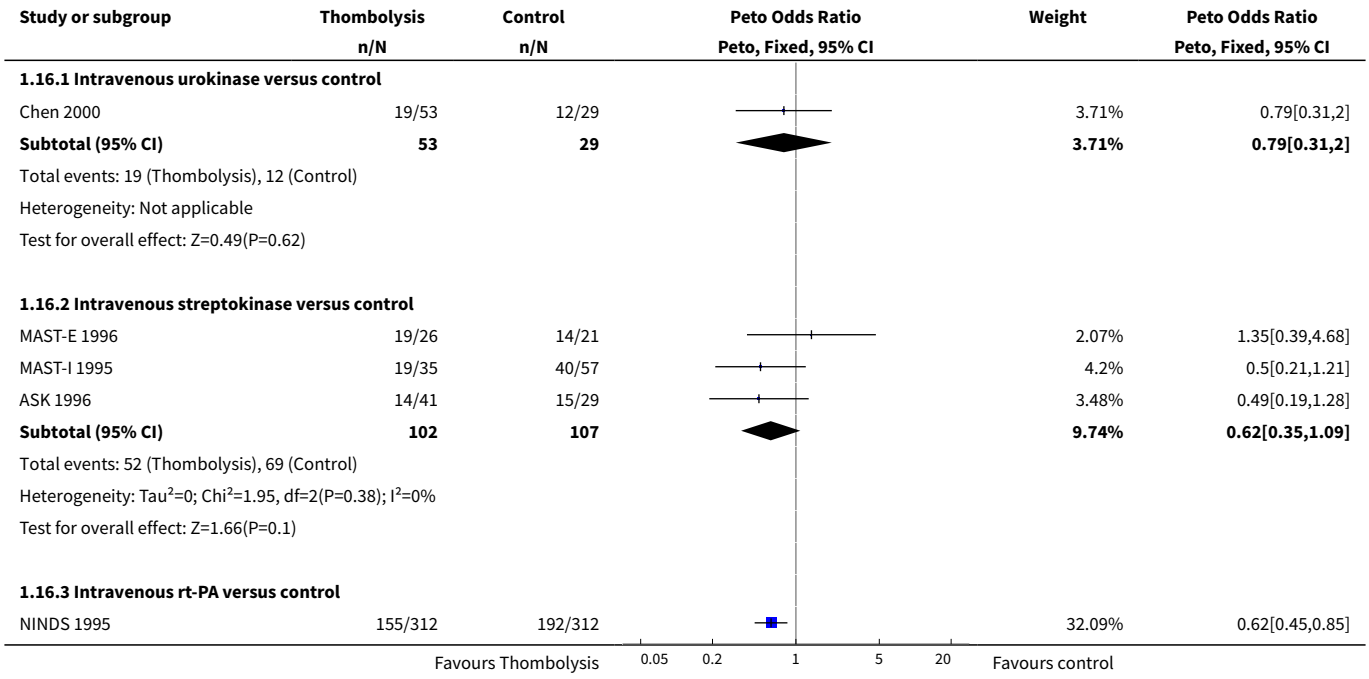
Analysis 1.15. Comparison 1 Any thrombolytic agent versus control, Outcome 15 Deaths from all causes ordered by stroke severity.

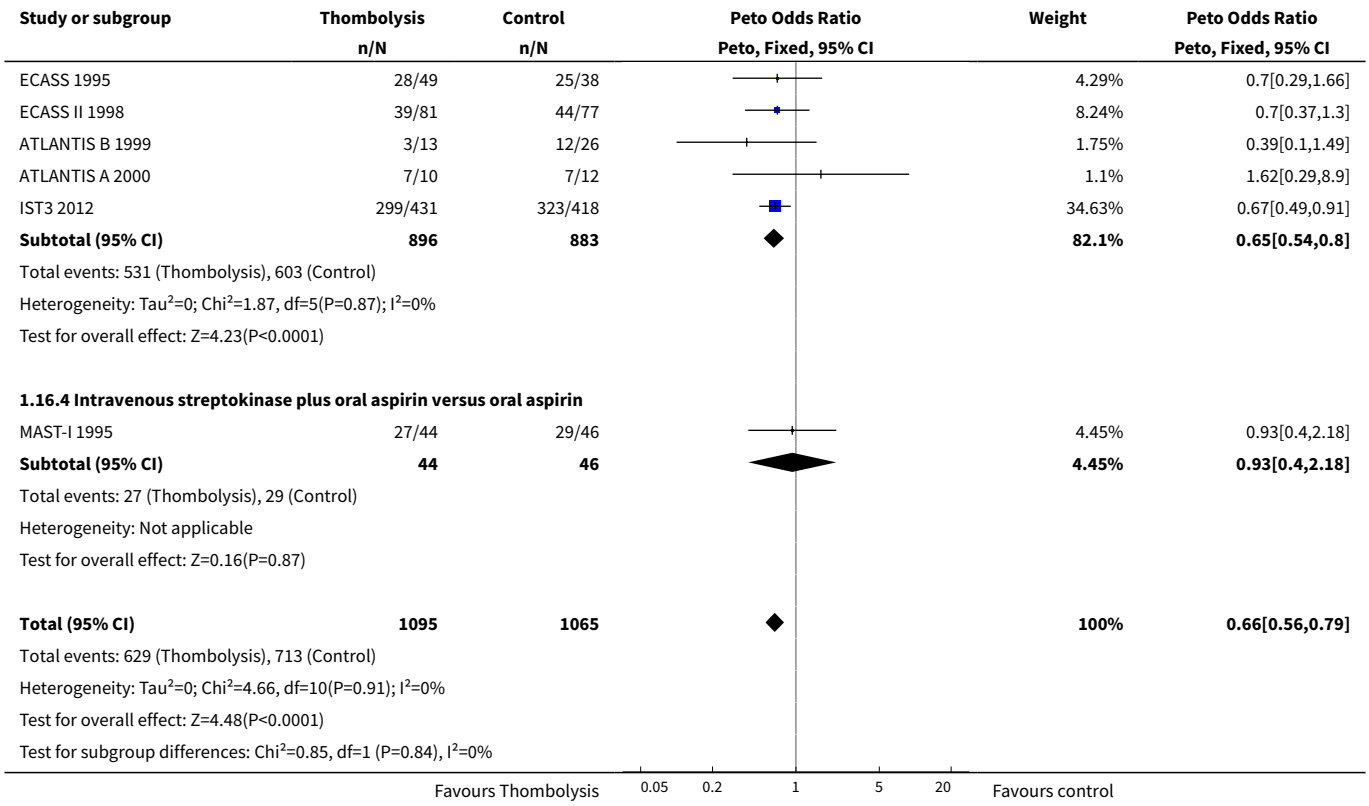
Study or subgroup	Thombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.15.1 Case fatality 0% - 19% in the control group					
Abe 1981	1/54	1/53		0.15%	0.98[0.06,15.9]
Atarashi 1985	7/192	4/94		0.69%	0.85[0.24,3.05]
Ohtomo 1985	3/169	6/181		0.64%	0.54[0.14,2.03]
Mori 1992	2/19	2/12		0.25%	0.59[0.07,4.91]
JTSG 1993	3/51	4/47		0.48%	0.68[0.15,3.12]
ECASS 1995	69/313	48/307		6.96%	1.52[1.02,2.27]
ECASS II 1998	43/409	42/391		5.57%	0.98[0.62,1.53]
ATLANTIS B 1999	33/307	21/306		3.61%	1.62[0.93,2.83]
ATLANTIS A 2000	16/71	5/71		1.32%	3.39[1.35,8.53]
Chen 2000	33/317	10/148		2.48%	1.54[0.79,3.03]
Wang 2003	5/67	3/33		0.48%	0.8[0.17,3.71]
DIAS 2005	7/75	0/27		0.38%	4.25[0.75,23.98]
DEDAS 2006	2/29	1/8		0.14%	0.48[0.03,8.14]
DIAS 2 2008	17/123	4/63		1.23%	2.1[0.81,5.47]
MELT 2007	3/57	2/57		0.35%	1.51[0.25,9.02]
EPITHET 2008	13/52	7/49		1.18%	1.95[0.74,5.17]
ECASS 3 2008	32/418	34/403		4.45%	0.9[0.54,1.49]
Subtotal (95% CI)	**2723**	**2250**		**30.35%**	**1.31[1.08,1.58]**
Total events: 289 (Thombolysis), 194 (Control)					





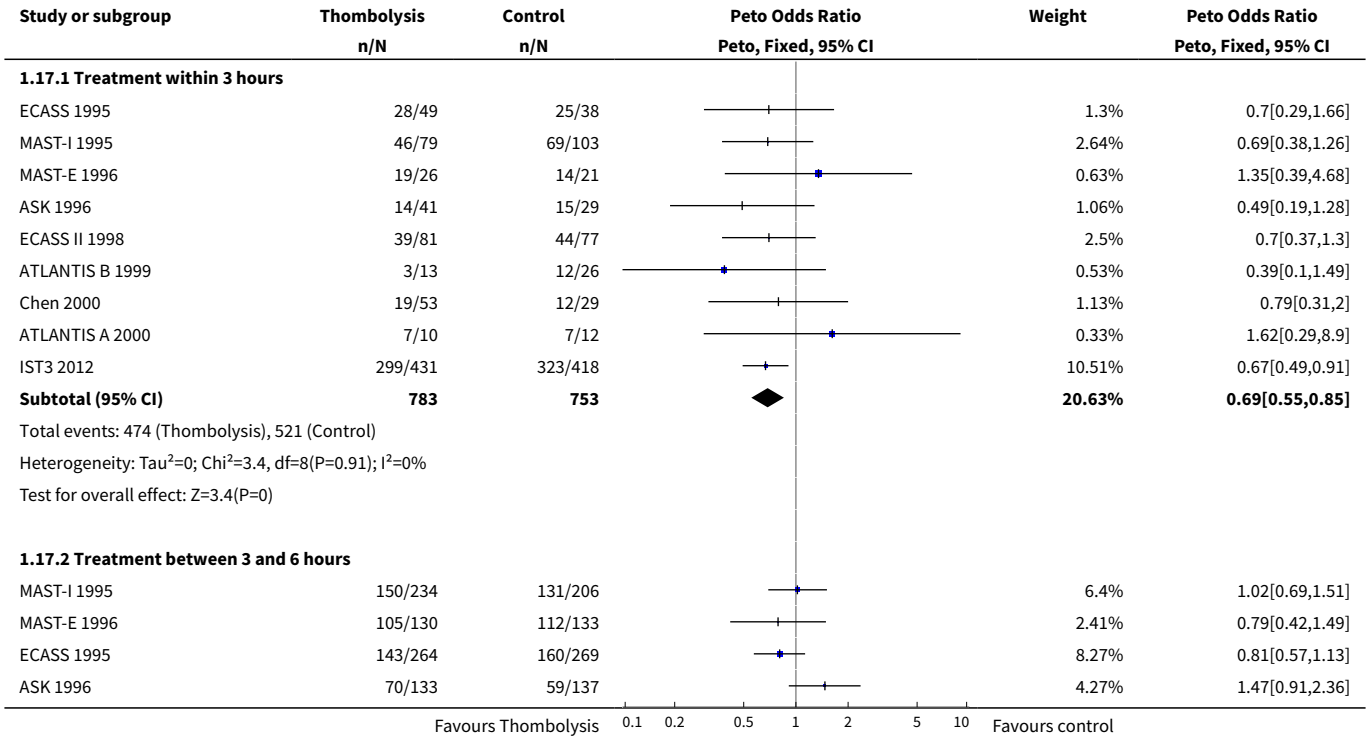
Analysis 1.16. Comparison 1 Any thrombolytic agent versus control, Outcome 16 Death or dependency at the end of follow-up: participants randomised within 3 hours of stroke.



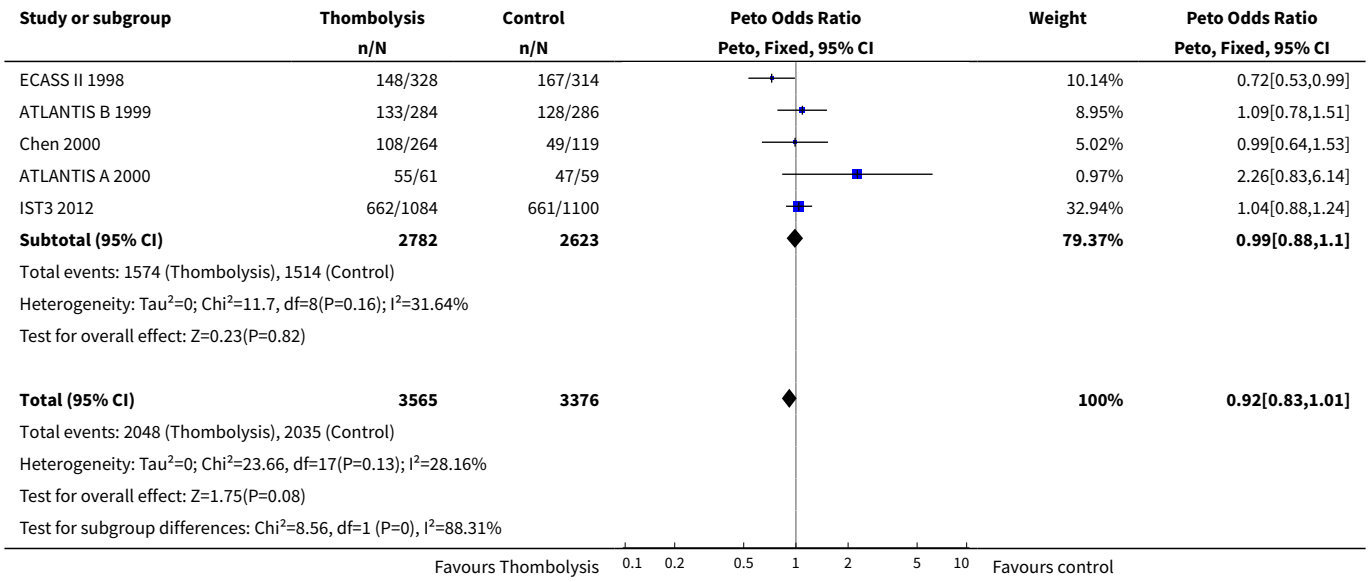


Study or subgroup	Thombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ECASS 1995	28/49	25/38		4.29%	0.7[0.29,1.66]
ECASS II 1998	39/81	44/77		8.24%	0.7[0.37,1.3]
ATLANTIS B 1999	3/13	12/26		1.75%	0.39[0.1,1.49]
ATLANTIS A 2000	7/10	7/12		1.1%	1.62[0.29,8.9]
IST3 2012	299/431	323/418		34.63%	0.67[0.49,0.91]
Subtotal (95% CI)	**896**	**883**		**82.1%**	**0.65[0.54,0.8]**
Total events: 531 (Thombolysis), 603 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.87, df=5(P=0.87); I^2=0%					
Test for overall effect: Z=4.23(P<0.0001)					
1.16.4 Intravenous streptokinase plus oral aspirin versus oral aspirin					
MAST-I 1995	27/44	29/46		4.45%	0.93[0.4,2.18]
Subtotal (95% CI)	**44**	**46**		**4.45%**	**0.93[0.4,2.18]**
Total events: 27 (Thombolysis), 29 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.16(P=0.87)					
Total (95% CI)	**1095**	**1065**		**100%**	**0.66[0.56,0.79]**
Total events: 629 (Thombolysis), 713 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.66, df=10(P=0.91); I^2=0%					
Test for overall effect: Z=4.48(P<0.0001)					
Test for subgroup differences: Chi^2=0.85, df=1 (P=0.84), I^2=0%					

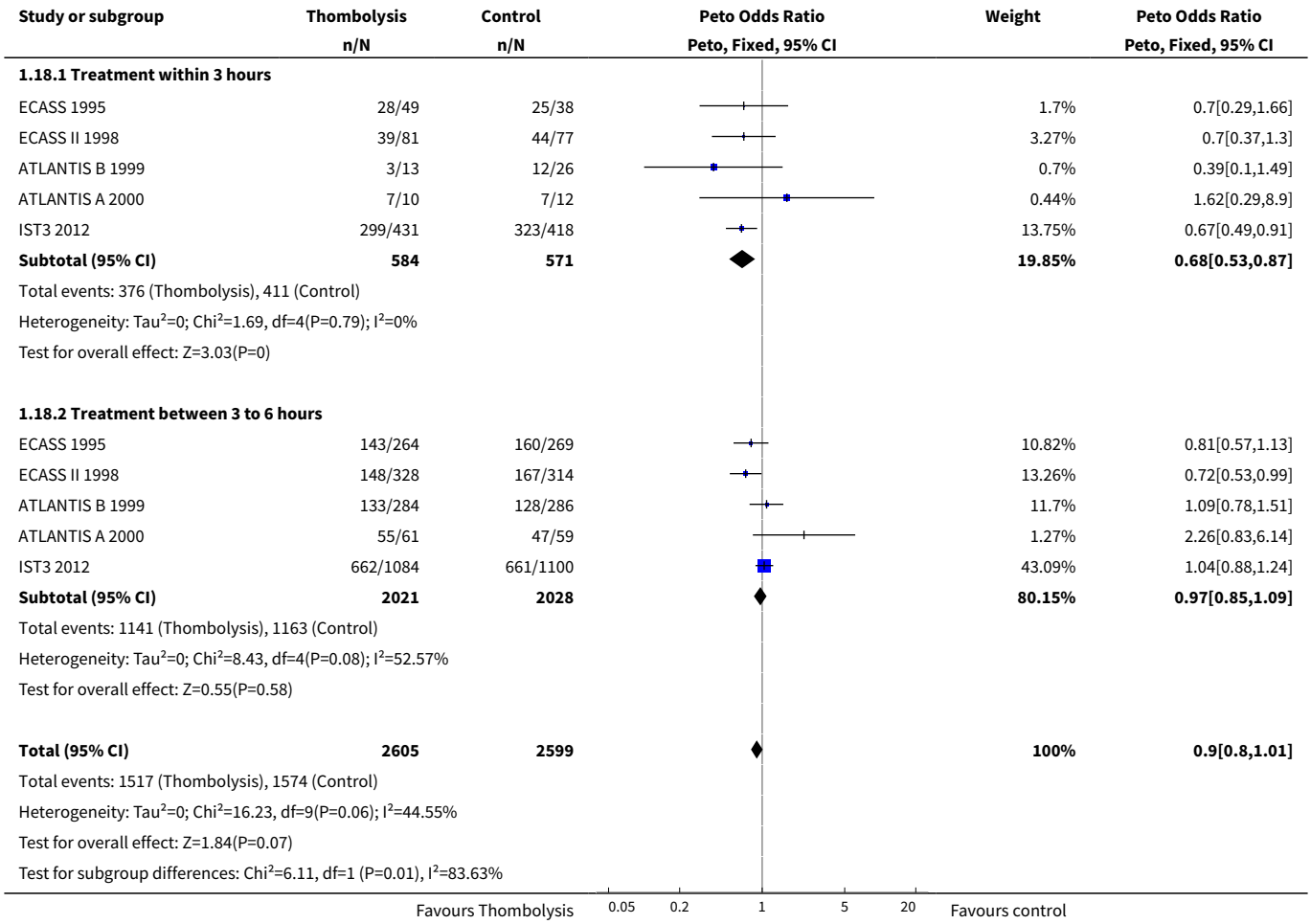
Analysis 1.17. Comparison 1 Any thrombolytic agent versus control, Outcome 17 Death or dependency by time to treatment up to 6 hours: all agents: only trials randomising in both 0 to 3 and 3 to 6 hour time windows.



Study or subgroup	Thombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.17.1 Treatment within 3 hours					
ECASS 1995	28/49	25/38		1.3%	0.7[0.29,1.66]
MAST-I 1995	46/79	69/103		2.64%	0.69[0.38,1.26]
MAST-E 1996	19/26	14/21		0.63%	1.35[0.39,4.68]
ASK 1996	14/41	15/29		1.06%	0.49[0.19,1.28]
ECASS II 1998	39/81	44/77		2.5%	0.7[0.37,1.3]
ATLANTIS B 1999	3/13	12/26		0.53%	0.39[0.1,1.49]
Chen 2000	19/53	12/29		1.13%	0.79[0.31,2]
ATLANTIS A 2000	7/10	7/12		0.33%	1.62[0.29,8.9]
IST3 2012	299/431	323/418		10.51%	0.67[0.49,0.91]
Subtotal (95% CI)	**783**	**753**		**20.63%**	**0.69[0.55,0.85]**
Total events: 474 (Thombolysis), 521 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.4, df=8(P=0.91); I^2=0%					
Test for overall effect: Z=3.4(P=0)					
1.17.2 Treatment between 3 and 6 hours					
MAST-I 1995	150/234	131/206		6.4%	1.02[0.69,1.51]
MAST-E 1996	105/130	112/133		2.41%	0.79[0.42,1.49]
ECASS 1995	143/264	160/269		8.27%	0.81[0.57,1.13]
ASK 1996	70/133	59/137		4.27%	1.47[0.91,2.36]

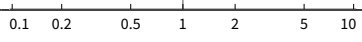


Analysis 1.18. Comparison 1 Any thrombolytic agent versus control, Outcome 18 Death or dependency by time to treatment up to 6 hours: rt-PA: only trials randomising in 0 - 3 and 3 - 6 hour windows.



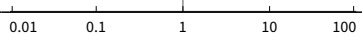
Analysis 1.19. Comparison 1 Any thrombolytic agent versus control, Outcome 19 Death or dependency by time to treatment up to 6 hours: rt-PA: all trials regardless of time window.

Study or subgroup	Thombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.19.1 Treatment within 3 hours					
ECASS 1995	28/49	25/38		1.31%	0.7[0.29,1.66]
NINDS 1995	155/312	192/312		9.8%	0.62[0.45,0.85]
ECASS II 1998	39/81	44/77		2.52%	0.7[0.37,1.3]
ATLANTIS B 1999	3/13	12/26		0.53%	0.39[0.1,1.49]
ATLANTIS A 2000	7/10	7/12		0.34%	1.62[0.29,8.9]
IST3 2012	299/431	323/418		10.57%	0.67[0.49,0.91]
Subtotal (95% CI)	**896**	**883**		**25.07%**	**0.65[0.54,0.8]**
Total events: 531 (Thombolysis), 603 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.87, df=5(P=0.87); I^2=0%					
Test for overall effect: Z=4.23(P<0.0001)					
1.19.2 Treatment between 3 and 6 hours					
ECASS 1995	143/264	160/269		8.32%	0.81[0.57,1.13]
ECASS II 1998	148/328	167/314		10.2%	0.72[0.53,0.99]
ATLANTIS B 1999	133/284	128/286		9%	1.09[0.78,1.51]
ATLANTIS A 2000	55/61	47/59		0.98%	2.26[0.83,6.14]
ECASS 3 2008	140/418	155/403		12.02%	0.81[0.61,1.07]
EPITHET 2008	18/37	26/43		1.27%	0.62[0.26,1.5]
IST3 2012	662/1084	661/1100		33.14%	1.04[0.88,1.24]
Subtotal (95% CI)	**2476**	**2474**		**74.93%**	**0.93[0.83,1.04]**
Total events: 1299 (Thombolysis), 1344 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.53, df=6(P=0.1); I^2=43.03%					
Test for overall effect: Z=1.23(P=0.22)					
Total (95% CI)	**3372**	**3357**		**100%**	**0.85[0.77,0.94]**
Total events: 1830 (Thombolysis), 1947 (Control)					
Heterogeneity: Tau^2=0; Chi^2=21.68, df=12(P=0.04); I^2=44.66%					
Test for overall effect: Z=3.18(P=0)					
Test for subgroup differences: Chi^2=9.28, df=1 (P=0), I^2=89.23%					

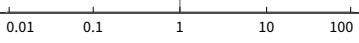


Analysis 1.20. Comparison 1 Any thrombolytic agent versus control, Outcome 20 Death or dependency by latest time to randomisation.

Study or subgroup	Thombolysis n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.20.1 3 hours					
NINDS 1995	155/312	192/312		8.55%	0.62[0.45,0.85]
Subtotal (95% CI)	**312**	**312**		**8.55%**	**0.62[0.45,0.85]**
Total events: 155 (Thombolysis), 192 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.97(P=0)					
1.20.2 4.5 hours					



Study or subgroup	Thombolysis n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
ASK 1996	84/174	74/166		6.17%	1.16[0.76,1.78]
ECASS 3 2008	140/418	155/403		9.45%	0.81[0.61,1.07]
Subtotal (95% CI)	**592**	**569**		**15.62%**	**0.93[0.66,1.32]**
Total events: 224 (Thombolysis), 229 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=1.94, df=1(P=0.16); I^2=48.41%					
Test for overall effect: Z=0.39(P=0.7)					
1.20.3 6 hours					
Mori 1992	11/19	10/12		0.55%	0.28[0.05,1.62]
Morris 1995	6/10	5/10		0.55%	1.5[0.26,8.82]
ECASS 1995	171/313	185/307		8.53%	0.79[0.58,1.09]
MAST-E 1996	124/156	126/154		4.19%	0.86[0.49,1.51]
MAST-I 1995	97/157	106/156		5.51%	0.76[0.48,1.21]
PROACT 1998	18/26	11/14		0.74%	0.61[0.13,2.82]
ECASS II 1998	187/409	211/391		9.66%	0.72[0.54,0.95]
ATLANTIS B 1999	141/307	135/306		8.55%	1.08[0.78,1.48]
PROACT 2 1999	73/121	44/59		3.06%	0.52[0.26,1.03]
ATLANTIS A 2000	64/71	56/71		1.72%	2.45[0.93,6.44]
Chen 2000	127/317	61/148		6.74%	0.95[0.64,1.42]
Wang 2003	29/67	26/33		1.72%	0.21[0.08,0.54]
MELT 2007	29/57	35/57		2.7%	0.65[0.31,1.37]
EPITHET 2008	29/51	29/49		2.42%	0.91[0.41,2.01]
IST3 2012	1152/1515	1200/1520		13.06%	0.85[0.71,1]
Subtotal (95% CI)	**3596**	**3287**		**69.72%**	**0.81[0.69,0.95]**
Total events: 2258 (Thombolysis), 2240 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=21.51, df=14(P=0.09); I^2=34.9%					
Test for overall effect: Z=2.57(P=0.01)					
1.20.4 9 hours					
DIAS 2005	46/75	21/27		1.56%	0.45[0.16,1.26]
DEDAS 2006	16/29	6/8		0.56%	0.41[0.07,2.38]
DIAS 2 2008	72/123	34/63		3.71%	1.2[0.65,2.22]
Subtotal (95% CI)	**227**	**98**		**5.83%**	**0.74[0.35,1.59]**
Total events: 134 (Thombolysis), 61 (Control)					
Heterogeneity: Tau^2=0.19; Chi^2=3.37, df=2(P=0.19); I^2=40.58%					
Test for overall effect: Z=0.76(P=0.45)					
1.20.5 24 hours					
AUST 2005	4/8	7/8		0.28%	0.14[0.01,1.76]
Subtotal (95% CI)	**8**	**8**		**0.28%**	**0.14[0.01,1.76]**
Total events: 4 (Thombolysis), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					
Total (95% CI)	**4735**	**4274**		**100%**	**0.81[0.71,0.92]**
Total events: 2775 (Thombolysis), 2729 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=32.42, df=21(P=0.05); I^2=35.22%					
Test for overall effect: Z=3.14(P=0)					
Test for subgroup differences: Chi^2=5.08, df=1 (P=0.28), I^2=21.29%					

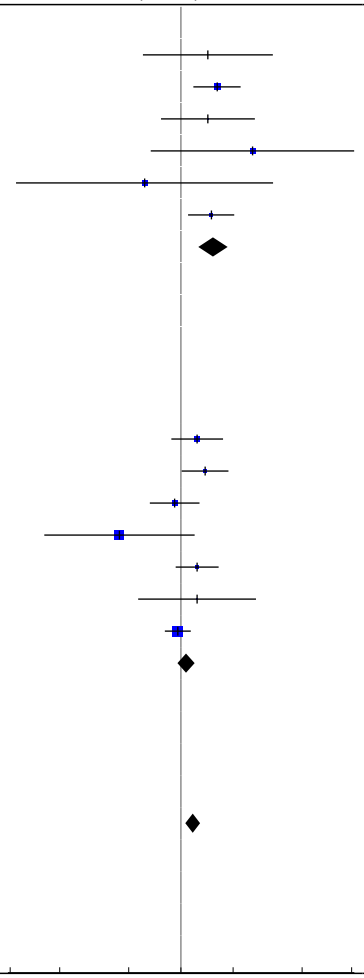


Favours Thombolysis

Favours control

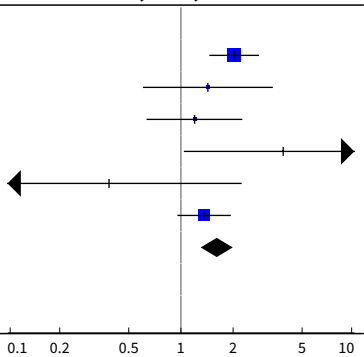
Analysis 1.21. Comparison 1 Any thrombolytic agent versus control, Outcome 21 Alive and independent (mRS 0 to 2) at end of follow-up, participants treated < 3 versus 3 to 6 hours, all trials regardless of latest time window.

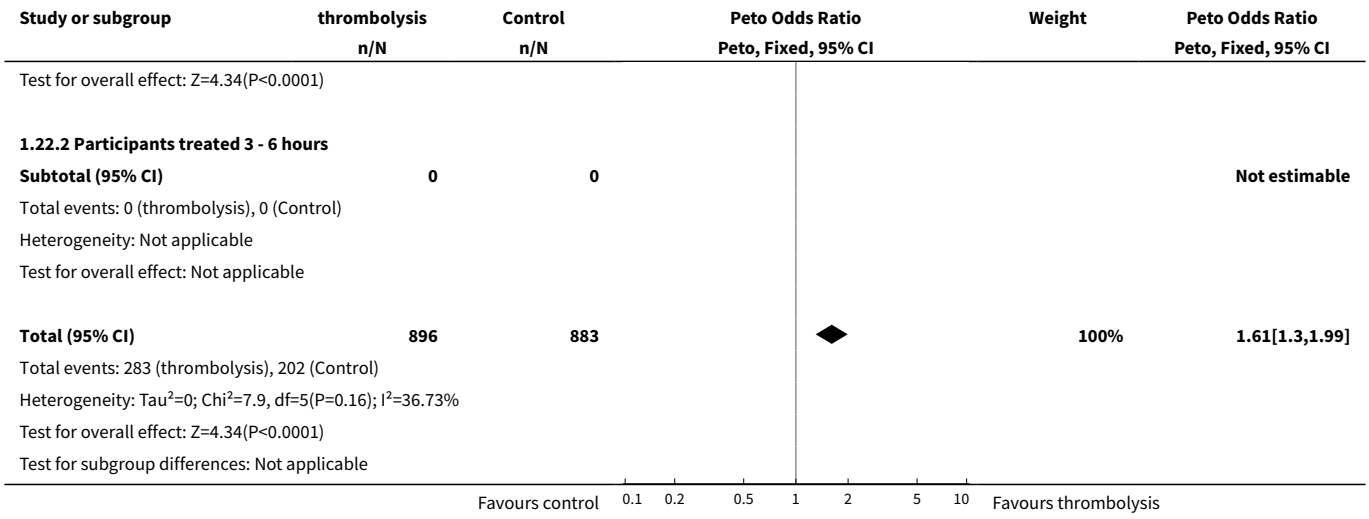
Study or subgroup	thrombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.21.1 Participants treated within three hours					
ECASS 1995	21/49	13/38		1.31%	1.43[0.6,3.39]
NINDS 1995	157/312	120/312		9.77%	1.62[1.18,2.21]
ECASS II 1998	42/81	33/77		2.51%	1.43[0.77,2.67]
ATLANTIS B 1999	10/13	14/26		0.53%	2.59[0.67,9.98]
ATLANTIS A 2000	3/10	5/12		0.33%	0.62[0.11,3.4]
IST3 2012	132/431	95/418		10.54%	1.5[1.1,2.03]
Subtotal (95% CI)	**896**	**883**		**24.99%**	**1.53[1.26,1.86]**
Total events: 365 (thrombolysis), 280 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.87, df=5(P=0.87); I^2=0%					
Test for overall effect: Z=4.23(P<0.0001)					
1.21.2 Participants treated 3 - 6 hours					
ECASS 1995	121/264	109/269		8.29%	1.24[0.88,1.75]
ECASS II 1998	180/328	147/314		10.17%	1.38[1.01,1.88]
ATLANTIS B 1999	151/284	158/286		8.97%	0.92[0.66,1.28]
ATLANTIS A 2000	6/61	12/59		0.98%	0.44[0.16,1.2]
ECASS 3 2008	278/418	248/403		11.98%	1.24[0.93,1.65]
EPITHET 2008	24/52	20/49		1.59%	1.24[0.57,2.71]
IST3 2012	422/1084	439/1100		33.04%	0.96[0.81,1.14]
Subtotal (95% CI)	**2491**	**2480**		**75.01%**	**1.07[0.96,1.2]**
Total events: 1182 (thrombolysis), 1133 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.86, df=6(P=0.13); I^2=39.14%					
Test for overall effect: Z=1.17(P=0.24)					
Total (95% CI)	**3387**	**3363**		**100%**	**1.17[1.06,1.29]**
Total events: 1547 (thrombolysis), 1413 (Control)					
Heterogeneity: Tau^2=0; Chi^2=21.22, df=12(P=0.05); I^2=43.44%					
Test for overall effect: Z=3.13(P=0)					
Test for subgroup differences: Chi^2=9.49, df=1 (P=0), I^2=89.46%					



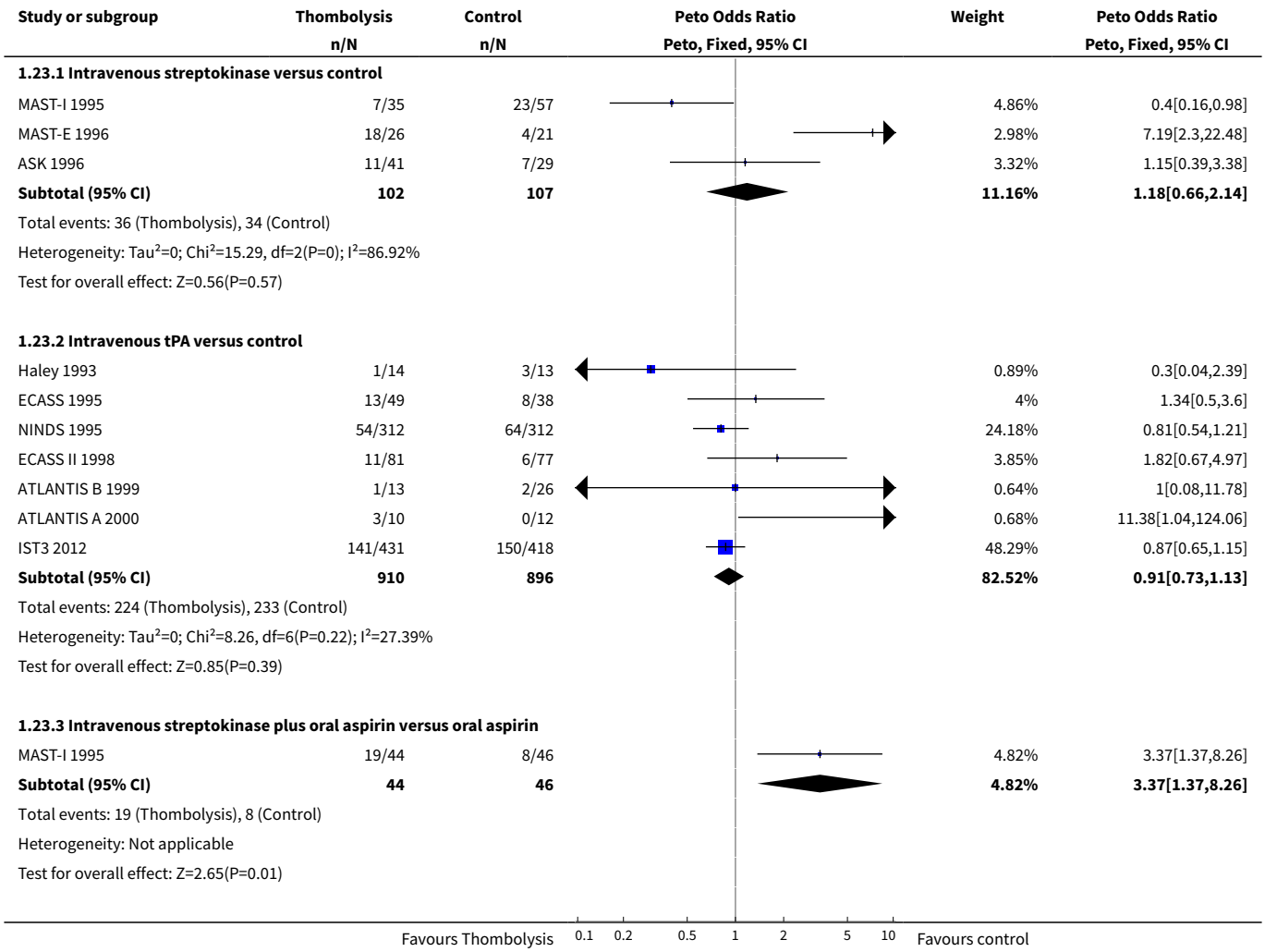
Analysis 1.22. Comparison 1 Any thrombolytic agent versus control, Outcome 22 Alive and favourable outcome (mRS 0 to 1) at end of follow-up, < 3 versus 3 - 6 hours, only trials randomising in both time windows.

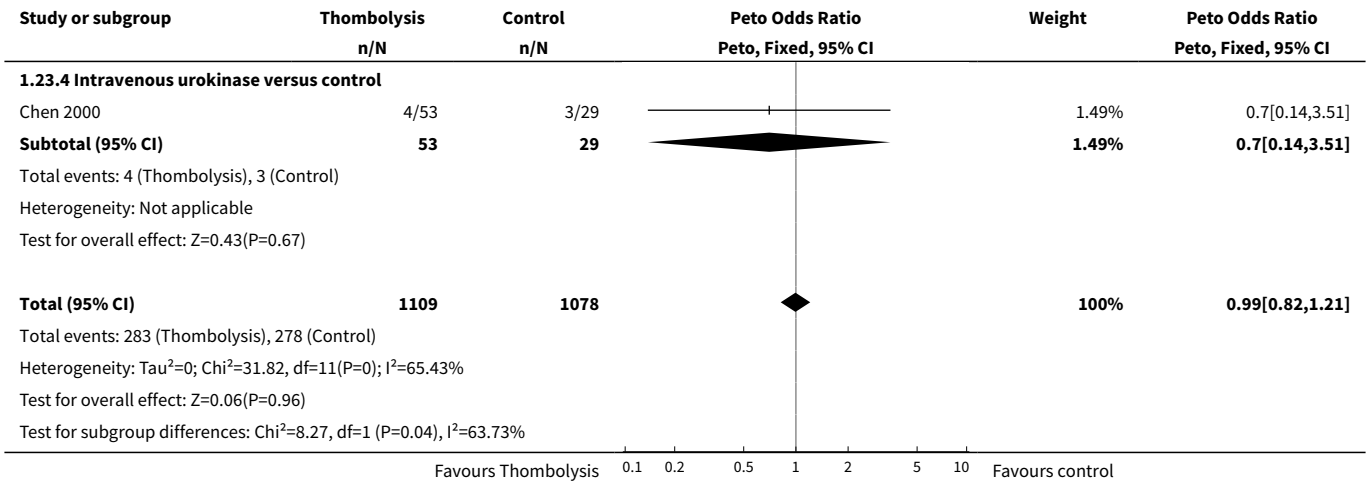
Study or subgroup	thrombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.22.1 Participants treated < 3 hours					
NINDS 1995	133/312	83/312		42.15%	2.03[1.46,2.82]
ECASS 1995	21/49	13/38		6.14%	1.43[0.6,3.39]
ECASS II 1998	34/81	29/77		11.35%	1.2[0.63,2.26]
ATLANTIS B 1999	9/13	9/26		2.63%	3.89[1.04,14.52]
ATLANTIS A 2000	2/10	5/12		1.48%	0.39[0.07,2.24]
IST3 2012	84/431	63/418		36.25%	1.36[0.95,1.94]
Subtotal (95% CI)	**896**	**883**		**100%**	**1.61[1.3,1.99]**
Total events: 283 (thrombolysis), 202 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.9, df=5(P=0.16); I^2=36.73%					



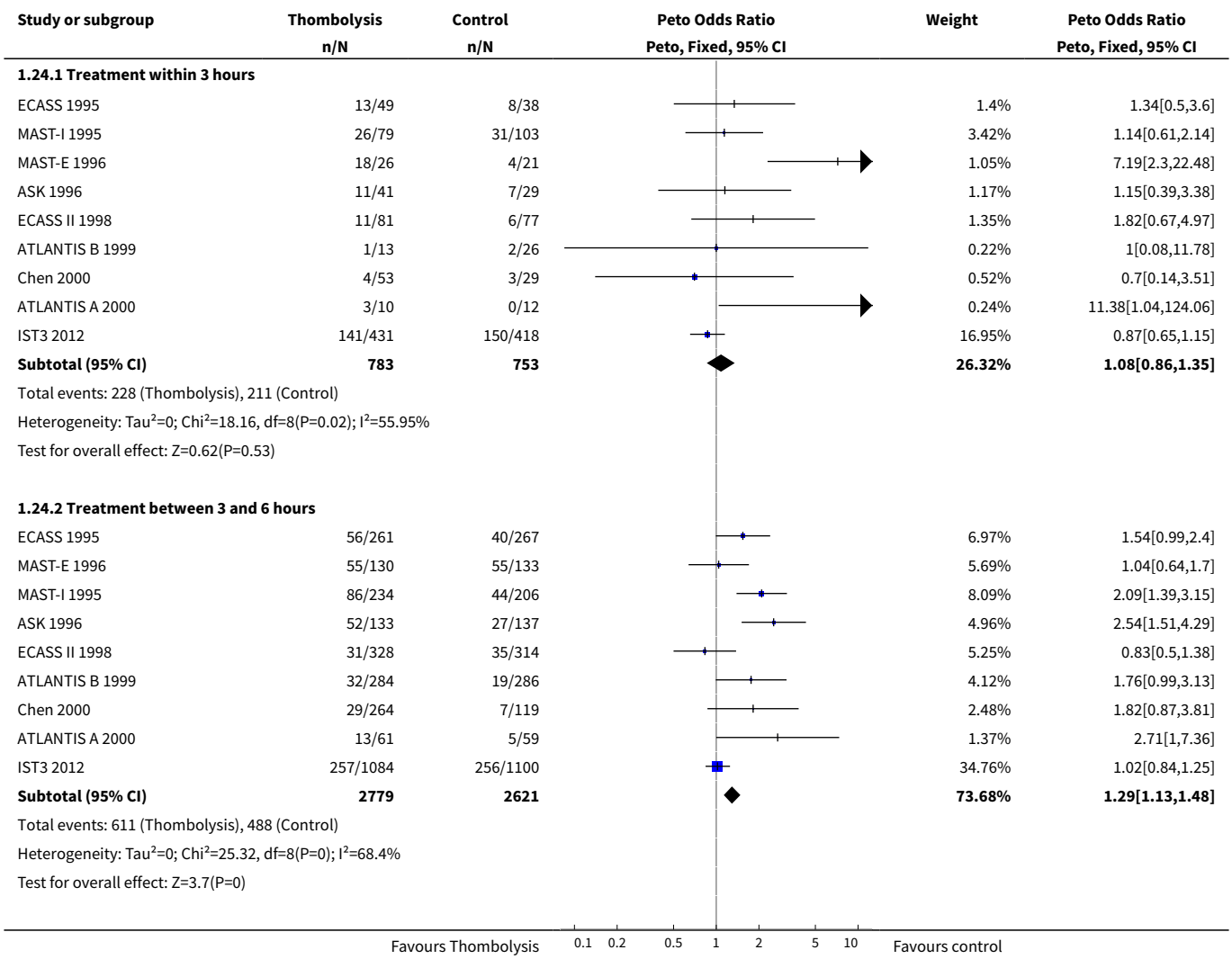


Analysis 1.23. Comparison 1 Any thrombolytic agent versus control, Outcome 23 Deaths from all causes during follow-up: participants randomised within 3 hours of stroke.





Analysis 1.24. Comparison 1 Any thrombolytic agent versus control, Outcome 24 Deaths by time to treatment up to 6 hours: all agents: only trials randomising in both 0 - 3 and 3 - 6 hour time windows.



Study or subgroup	Thombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Total (95% CI)	**3562**	**3374**		**100%**	**1.23[1.1,1.38]**
Total events: 839 (Thombolysis), 699 (Control)					
Heterogeneity: Tau^2=0; Chi^2=45.34, df=17(P=0); I^2=62.51%					
Test for overall effect: Z=3.5(P=0)					
Test for subgroup differences: Chi^2=1.86, df=1 (P=0.17), I^2=46.19%					

Favours Thombolysis 0.1 0.2 0.5 1 2 5 10 Favours control

Analysis 1.25. Comparison 1 Any thrombolytic agent versus control, Outcome 25 Deaths by time to treatment up to 6 hours: rt-PA: only trials randomising in both 0 to 3 and 3 to 6 hour time windows.

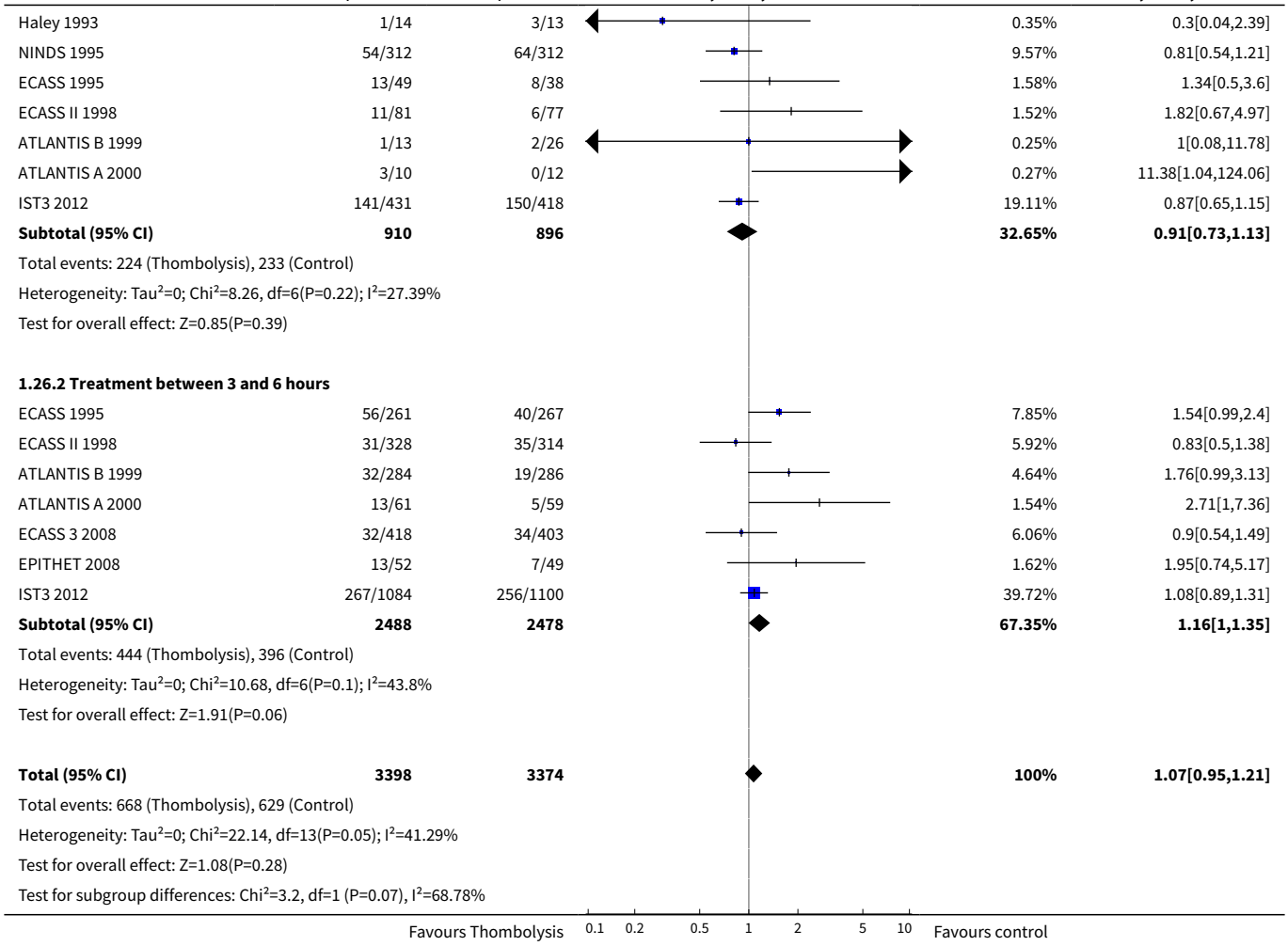
Study or subgroup	Thombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.25.1 Treatment within 3 hours					
ECASS 1995	13/49	8/38		1.92%	1.34[0.5,3.6]
ECASS II 1998	11/81	6/77		1.85%	1.82[0.67,4.97]
ATLANTIS B 1999	1/13	2/26		0.31%	1[0.08,11.78]
ATLANTIS A 2000	3/10	0/12		0.33%	11.38[1.04,124.06]
IST3 2012	141/431	150/418		23.19%	0.87[0.65,1.15]
Subtotal (95% CI)	**584**	**571**		**27.59%**	**0.97[0.75,1.26]**
Total events: 169 (Thombolysis), 166 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.59, df=4(P=0.16); I^2=39.33%					
Test for overall effect: Z=0.22(P=0.83)					
1.25.2 Treatment between 3 and 6 hours					
ECASS 1995	56/261	40/267		9.53%	1.54[0.99,2.4]
ECASS II 1998	31/328	35/314		7.18%	0.83[0.5,1.38]
ATLANTIS B 1999	32/284	19/286		5.63%	1.76[0.99,3.13]
ATLANTIS A 2000	13/61	5/59		1.87%	2.71[1,7.36]
IST3 2012	267/1084	256/1100		48.2%	1.08[0.89,1.31]
Subtotal (95% CI)	**2018**	**2026**		**72.41%**	**1.17[1,1.38]**
Total events: 399 (Thombolysis), 355 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.59, df=4(P=0.07); I^2=53.43%					
Test for overall effect: Z=1.94(P=0.05)					
Total (95% CI)	**2602**	**2597**		**100%**	**1.11[0.97,1.28]**
Total events: 568 (Thombolysis), 521 (Control)					
Heterogeneity: Tau^2=0; Chi^2=16.63, df=9(P=0.05); I^2=45.87%					
Test for overall effect: Z=1.53(P=0.12)					
Test for subgroup differences: Chi^2=1.44, df=1 (P=0.23), I^2=30.76%					

Favours Thombolysis 0.1 0.2 0.5 1 2 5 10 Favours control

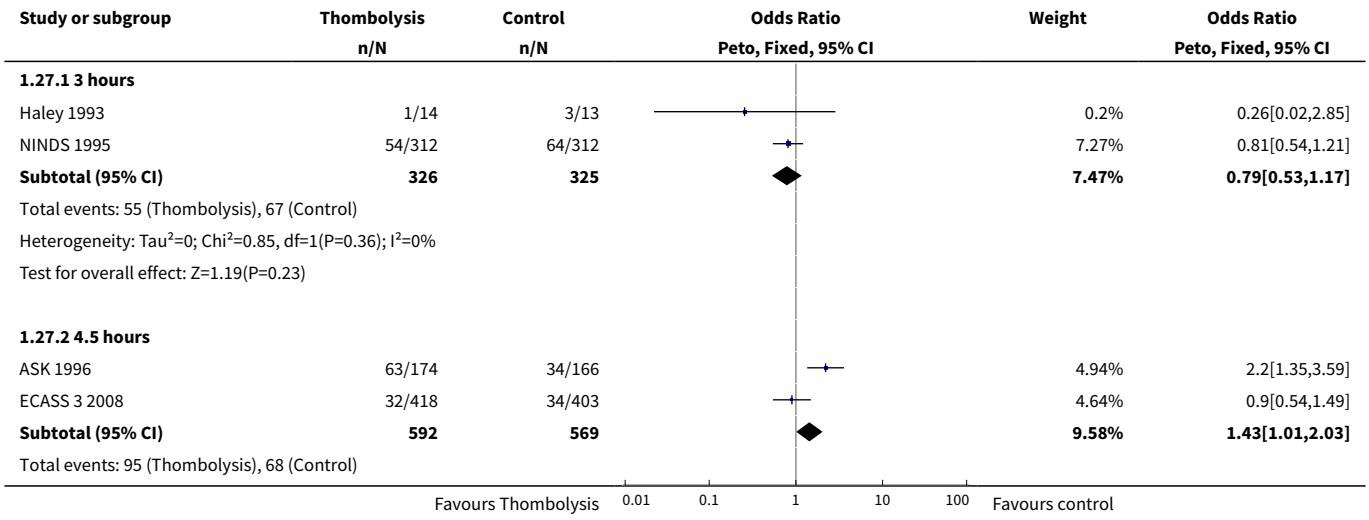
Analysis 1.26. Comparison 1 Any thrombolytic agent versus control, Outcome 26 Deaths by time to treatment up to 6 hours: rt-PA: all trials regardless of time window.

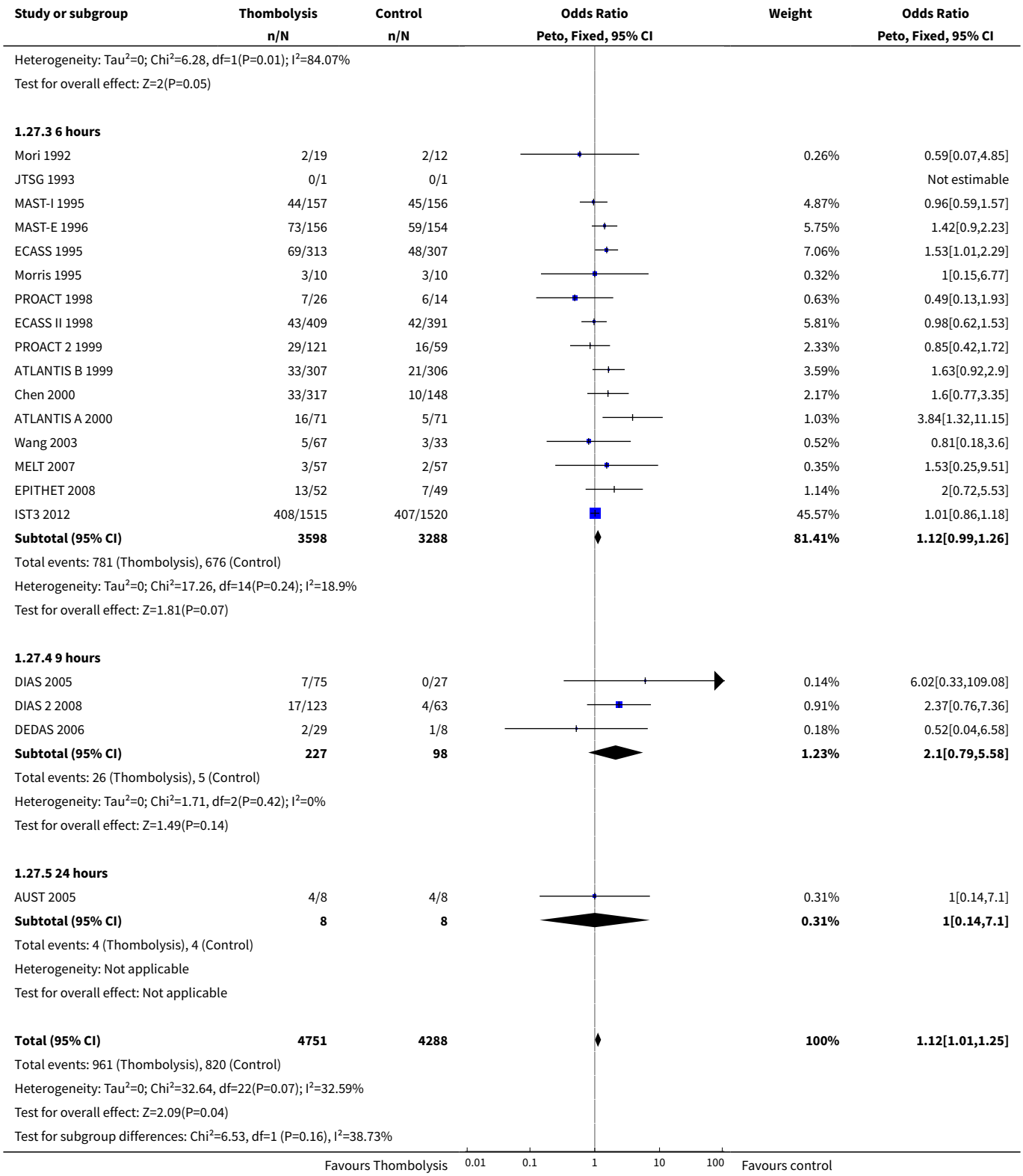
Study or subgroup	Thombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.26.1 Treatment within 3 hours					

Favours Thombolysis 0.1 0.2 0.5 1 2 5 10 Favours control



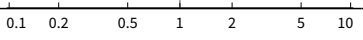
Analysis 1.27. Comparison 1 Any thrombolytic agent versus control, Outcome 27 Death by latest time to treatment.





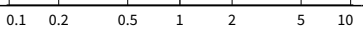
Analysis 1.28. Comparison 1 Any thrombolytic agent versus control, Outcome 28 Symptomatic intracranial haemorrhage by time to treatment up to 6 hours: rt-PA: only trials randomising in both 0 - 3 and 3 - 6 hour time windows..

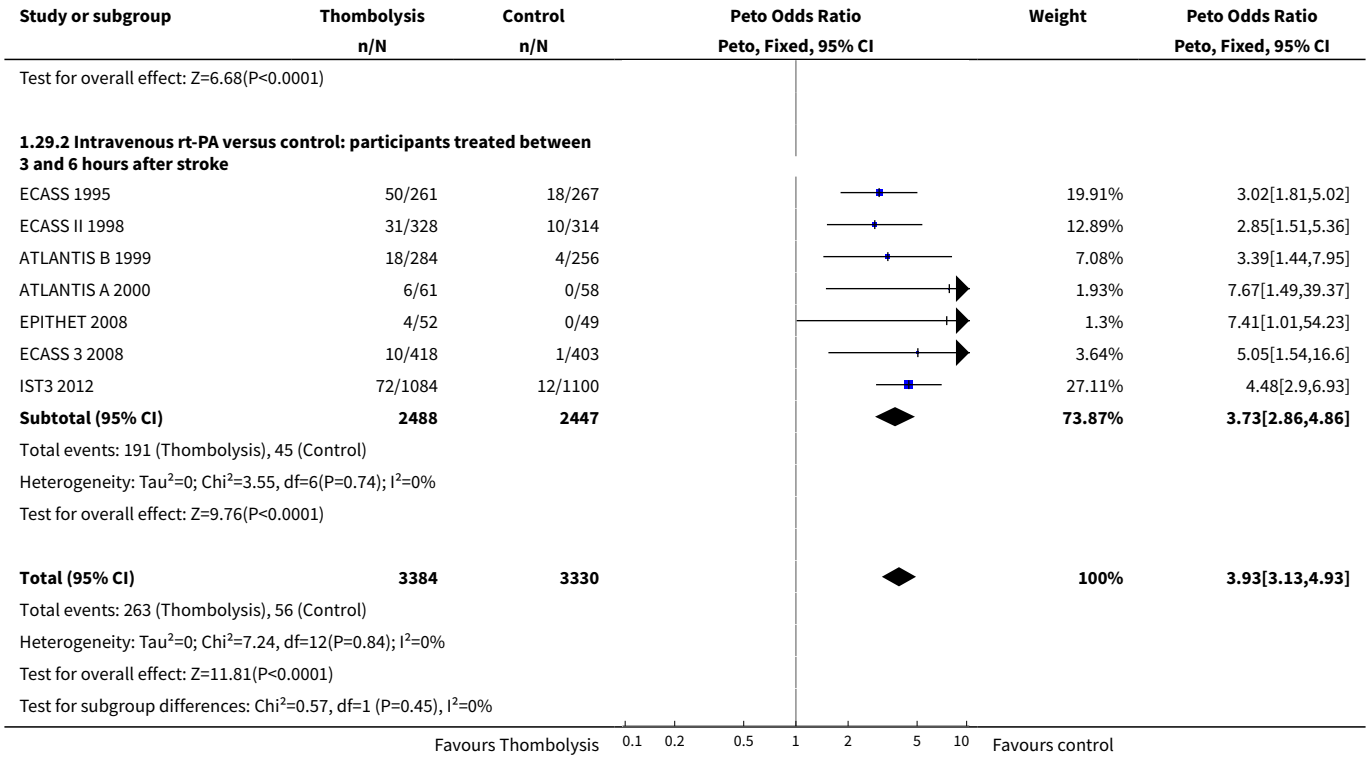
Study or subgroup	Thombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.28.1 Intravenous rt-PA versus control: participants treated within 3 hours of stroke					
ECASS 1995	12/49	2/38		4.46%	4.09[1.3,12.86]
ECASS II 1998	5/81	3/77		2.92%	1.6[0.39,6.61]
ATLANTIS B 1999	1/13	0/26		0.34%	20.09[0.31,1283.97]
ATLANTIS A 2000	2/10	0/12		0.72%	10.07[0.58,174.52]
IST3 2012	32/431	4/418		13.17%	4.91[2.52,9.57]
Subtotal (95% CI)	**584**	**571**		**21.61%**	**4.25[2.53,7.16]**
Total events: 52 (Thombolysis), 9 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.89, df=4(P=0.58); I^2=0%					
Test for overall effect: Z=5.45(P<0.0001)					
1.28.2 Intravenous rt-PA versus control: participants treated between 3 and 6 hours after stroke					
ECASS 1995	50/261	18/267		22.65%	3.02[1.81,5.02]
ECASS II 1998	31/328	10/314		14.66%	2.85[1.51,5.36]
ATLANTIS B 1999	18/284	4/256		8.05%	3.39[1.44,7.95]
ATLANTIS A 2000	6/61	0/58		2.19%	7.67[1.49,39.37]
IST3 2012	72/1084	12/1100		30.84%	4.48[2.9,6.93]
Subtotal (95% CI)	**2018**	**1995**		**78.39%**	**3.62[2.76,4.76]**
Total events: 177 (Thombolysis), 44 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.8, df=4(P=0.59); I^2=0%					
Test for overall effect: Z=9.22(P<0.0001)					
Total (95% CI)	**2602**	**2566**		**100%**	**3.75[2.94,4.78]**
Total events: 229 (Thombolysis), 53 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.98, df=9(P=0.74); I^2=0%					
Test for overall effect: Z=10.7(P<0.0001)					
Test for subgroup differences: Chi^2=0.29, df=1 (P=0.59), I^2=0%					



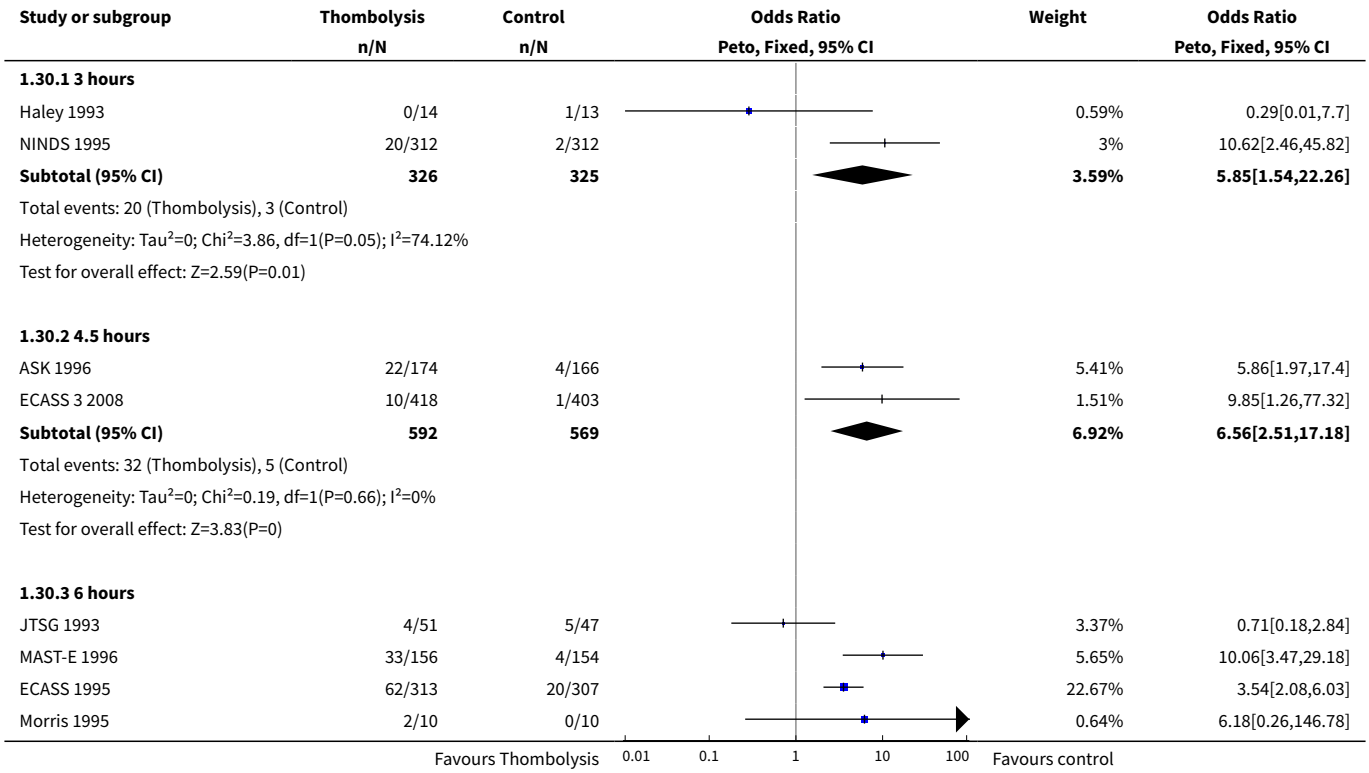
Analysis 1.29. Comparison 1 Any thrombolytic agent versus control, Outcome 29 Symptomatic intracranial haemorrhage by time to treatment up to 6 hours: rt-PA: all trials regardless of time window.

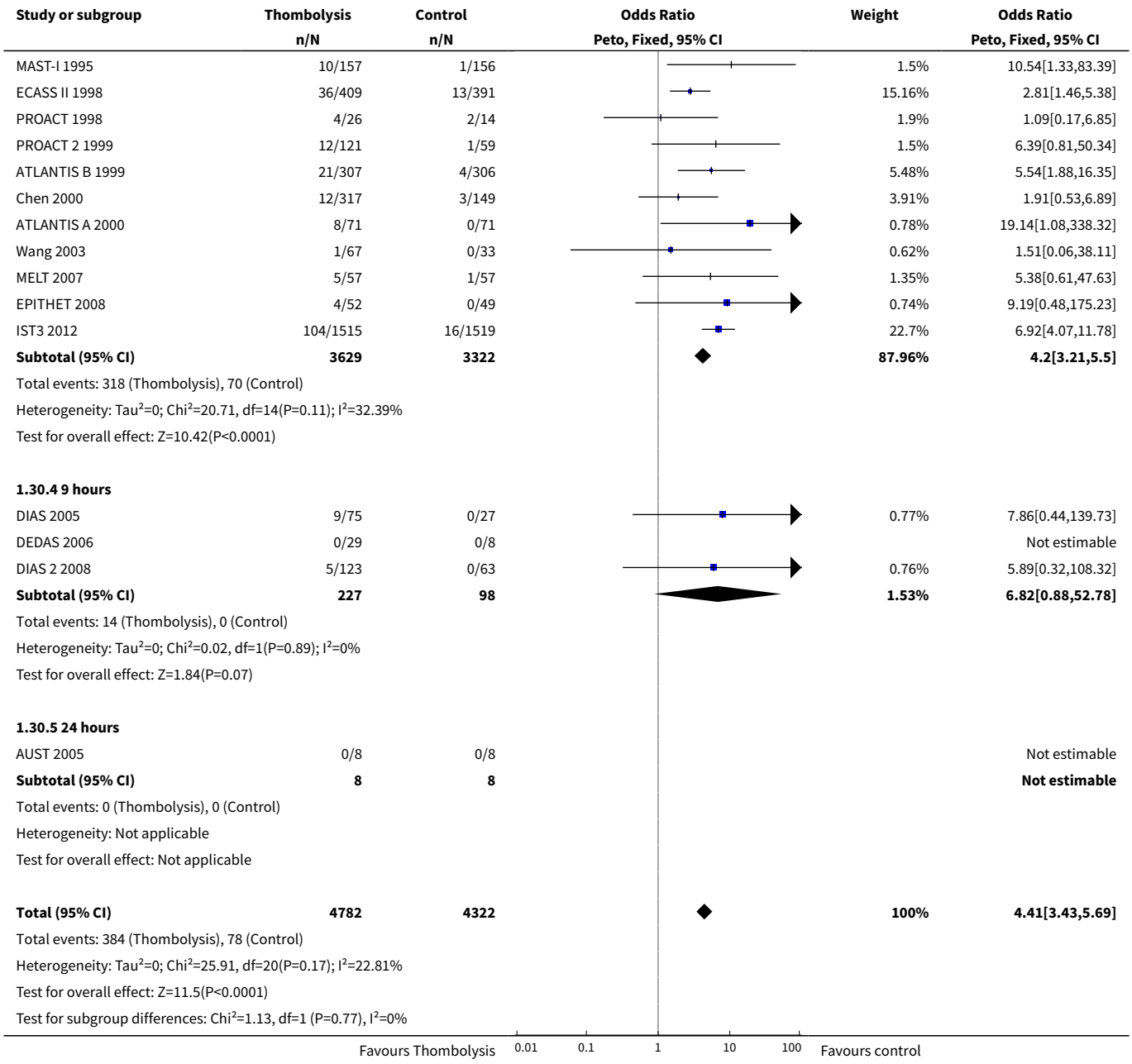
Study or subgroup	Thombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.29.1 Intravenous rt-PA versus control: participants treated within 3 hours of stroke					
ECASS 1995	12/49	2/38		3.92%	4.09[1.3,12.86]
NINDS 1995	20/312	2/312		7.13%	5.44[2.32,12.73]
ECASS II 1998	5/81	3/77		2.56%	1.6[0.39,6.61]
ATLANTIS B 1999	1/13	0/26		0.3%	20.09[0.31,1283.97]
ATLANTIS A 2000	2/10	0/12		0.63%	10.07[0.58,174.52]
IST3 2012	32/431	4/418		11.58%	4.91[2.52,9.57]
Subtotal (95% CI)	**896**	**883**		**26.13%**	**4.55[2.92,7.09]**
Total events: 72 (Thombolysis), 11 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.12, df=5(P=0.68); I^2=0%					



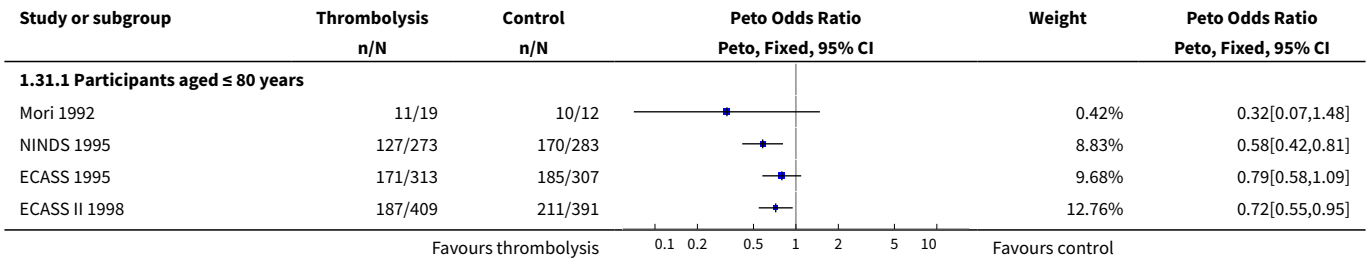


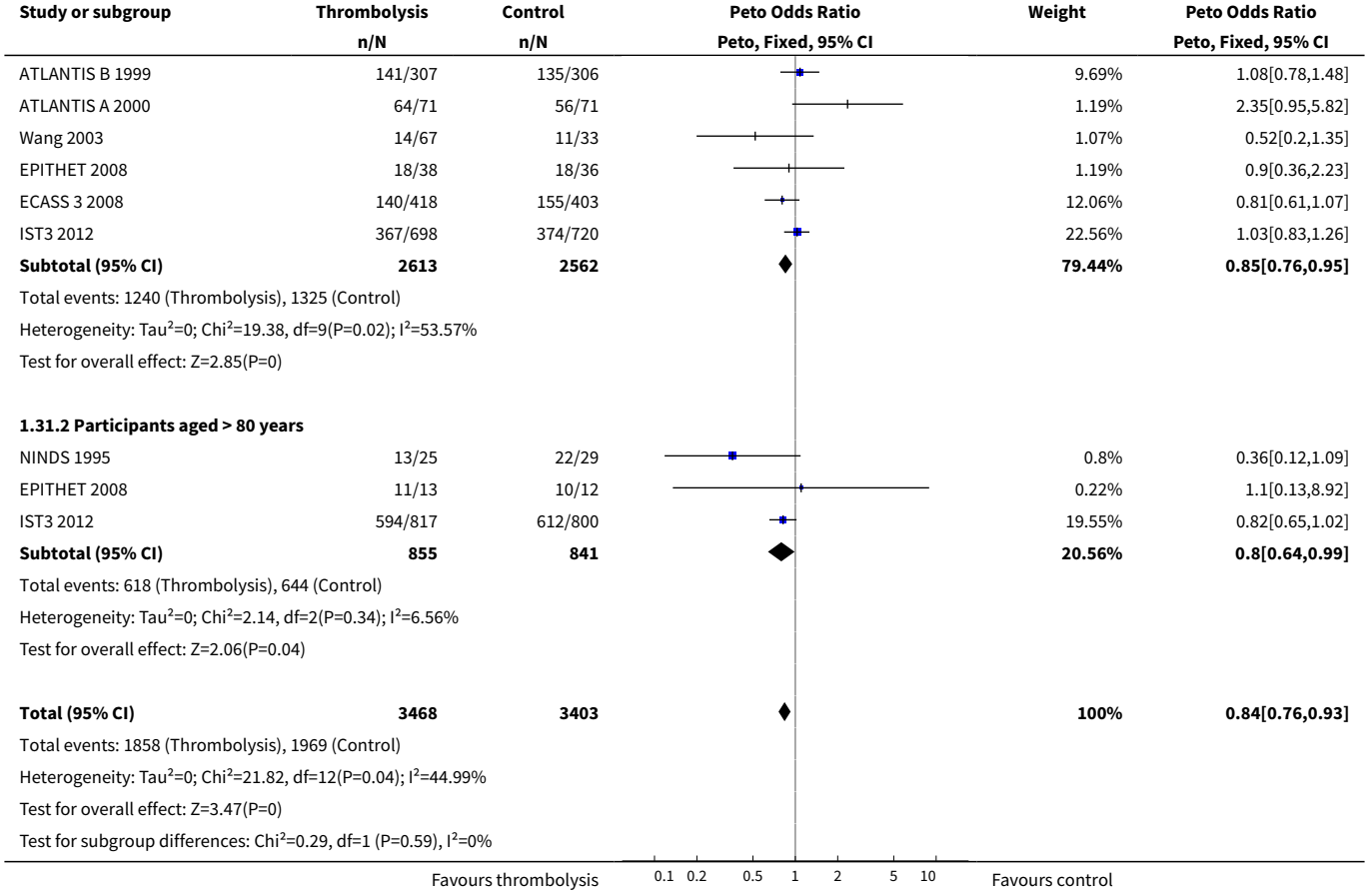
Analysis 1.30. Comparison 1 Any thrombolytic agent versus control, Outcome 30 Symptomatic intracranial haemorrhage by latest time to treatment.



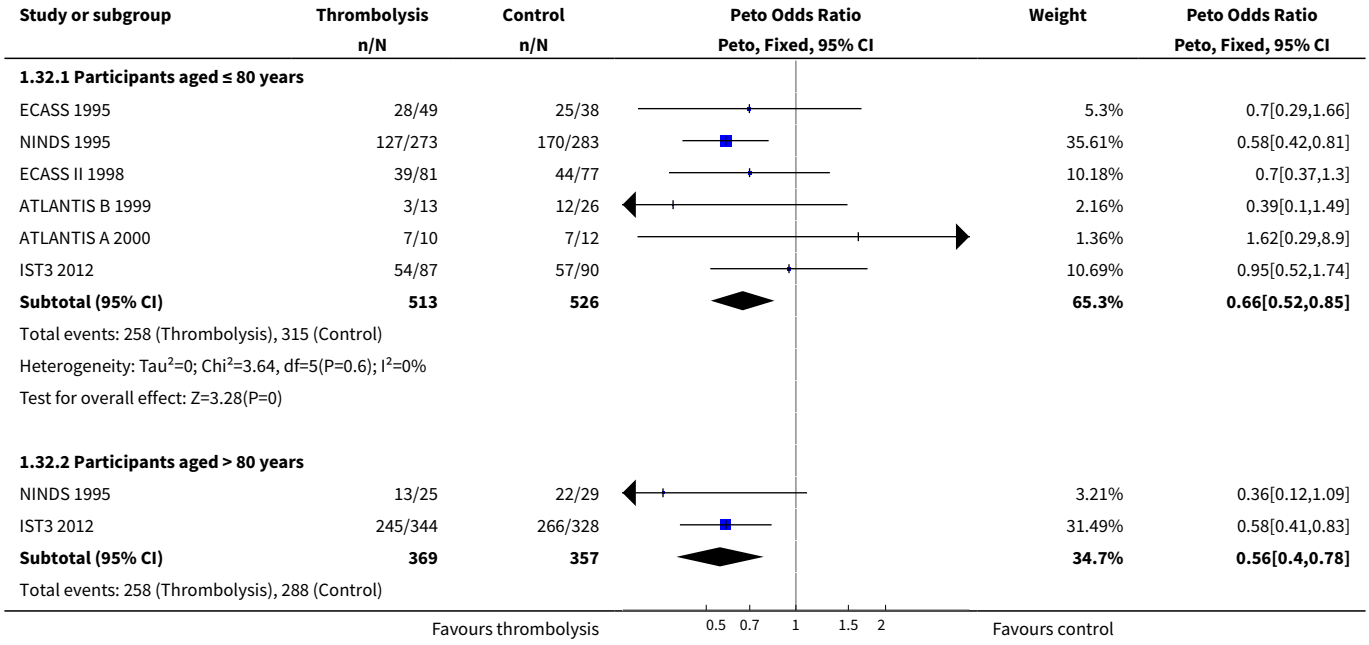


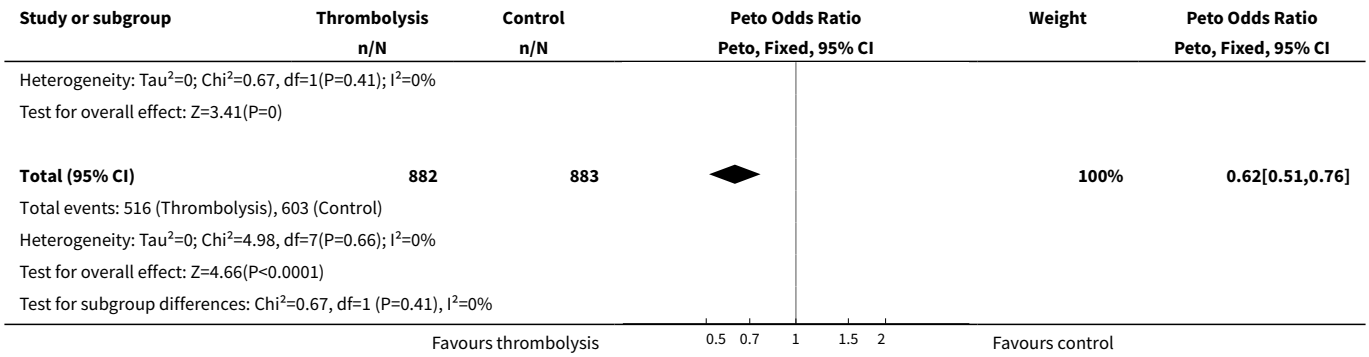
Analysis 1.31. Comparison 1 Any thrombolytic agent versus control, Outcome 31 Death or dependency (mRS 3 to 6) by the end of follow-up; participants treated up to 6 hours aged ≤ 80 years versus > 80 years.



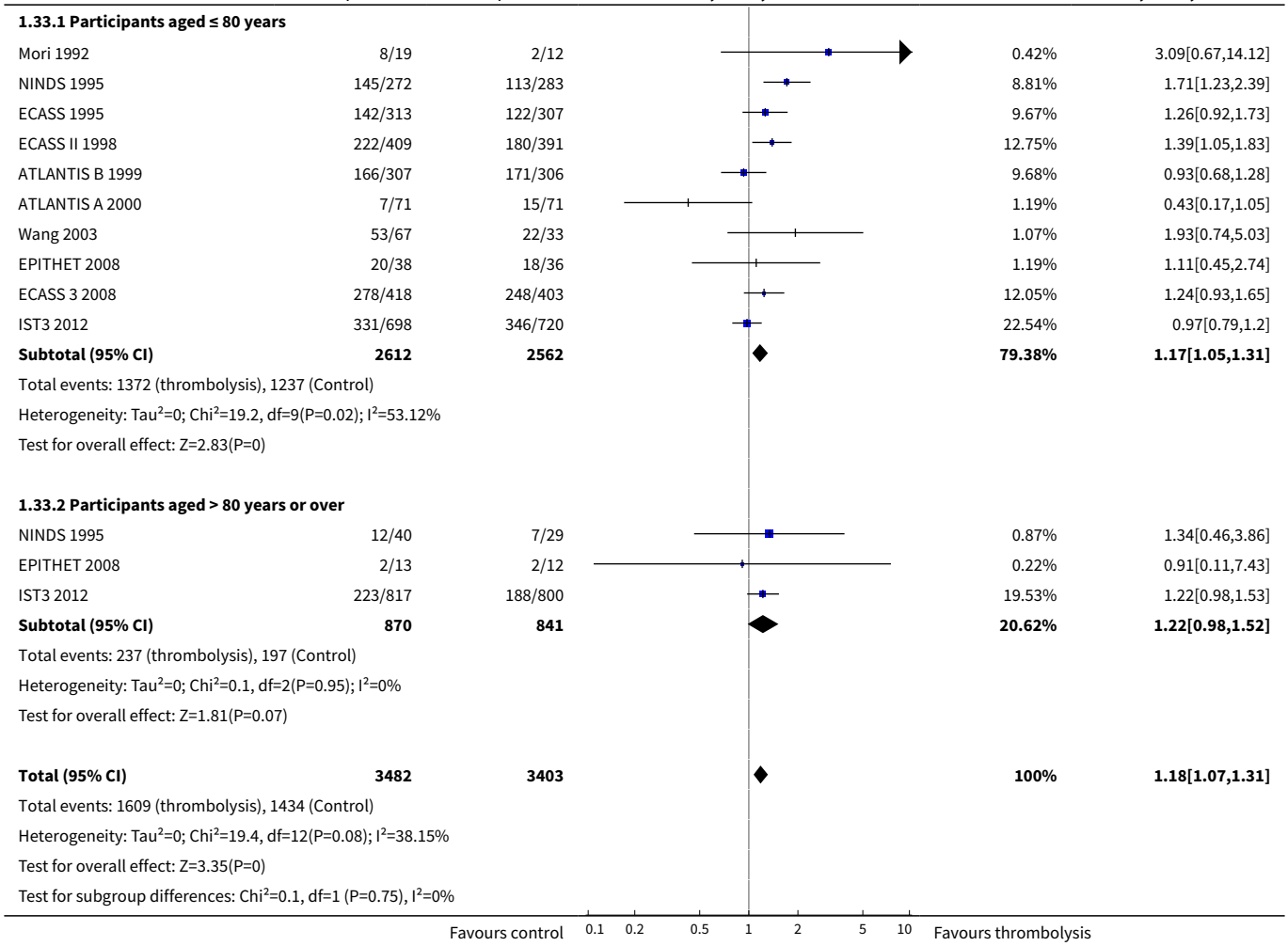


Analysis 1.32. Comparison 1 Any thrombolytic agent versus control, Outcome 32 Death or dependency (mRS 3 to 6) by the end of follow-up, participants treated within 3 hours aged ≤ 80 years versus > 80 years.



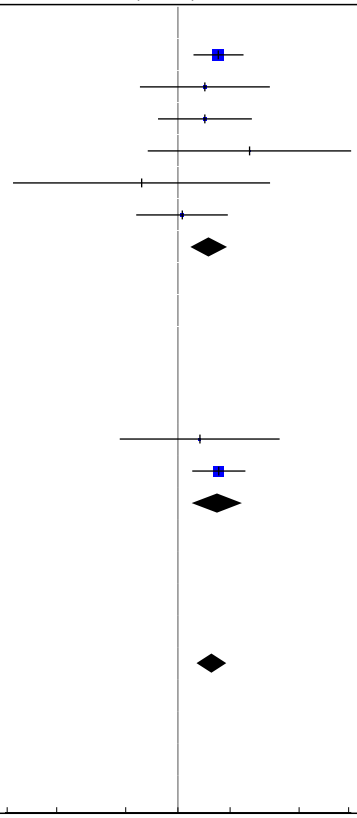


Analysis 1.33. Comparison 1 Any thrombolytic agent versus control, Outcome 33 Alive and independent (mRS 0 to 2) at end of follow-up, participants treated up to 6 hours aged ≤ 80 years versus > 80 years.



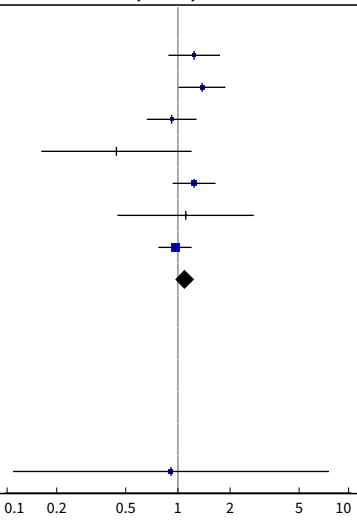
Analysis 1.34. Comparison 1 Any thrombolytic agent versus control, Outcome 34 Alive and independent (mRS 0 to 2) at end of folllow-up, participants treated within 3 hours, aged ≤ 80 years versus > 80 years.

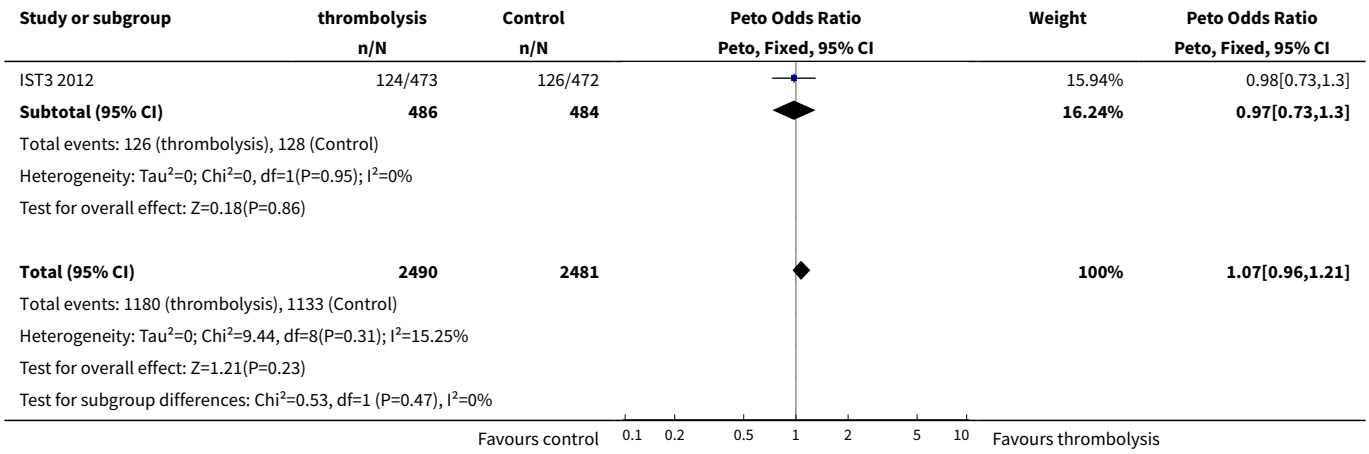
Study or subgroup	thrombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.34.1 Participants aged ≤ 80 years versus					
NINDS 1995	145/272	113/283		35.45%	1.71[1.23,2.39]
ECASS 1995	21/49	13/38		5.29%	1.43[0.6,3.39]
ECASS II 1998	42/81	33/77		10.16%	1.43[0.77,2.67]
ATLANTIS B 1999	10/13	14/26		2.16%	2.59[0.67,9.98]
ATLANTIS A 2000	3/10	5/12		1.36%	0.62[0.11,3.4]
IST3 2012	33/87	33/90		10.67%	1.06[0.57,1.94]
Subtotal (95% CI)	**512**	**526**		**65.09%**	**1.5[1.18,1.92]**
Total events: 254 (thrombolysis), 211 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.58, df=5(P=0.61); I^2=0%					
Test for overall effect: Z=3.25(P=0)					
1.34.2 Participants aged > 80 years and over					
NINDS 1995	12/40	7/29		3.49%	1.34[0.46,3.86]
IST3 2012	99/344	62/328		31.42%	1.72[1.21,2.45]
Subtotal (95% CI)	**384**	**357**		**34.91%**	**1.68[1.2,2.34]**
Total events: 111 (thrombolysis), 69 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.66); I^2=0%					
Test for overall effect: Z=3.01(P=0)					
Total (95% CI)	**896**	**883**		**100%**	**1.56[1.28,1.9]**
Total events: 365 (thrombolysis), 280 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.03, df=7(P=0.78); I^2=0%					
Test for overall effect: Z=4.4(P<0.0001)					
Test for subgroup differences: Chi^2=0.26, df=1 (P=0.61), I^2=0%					



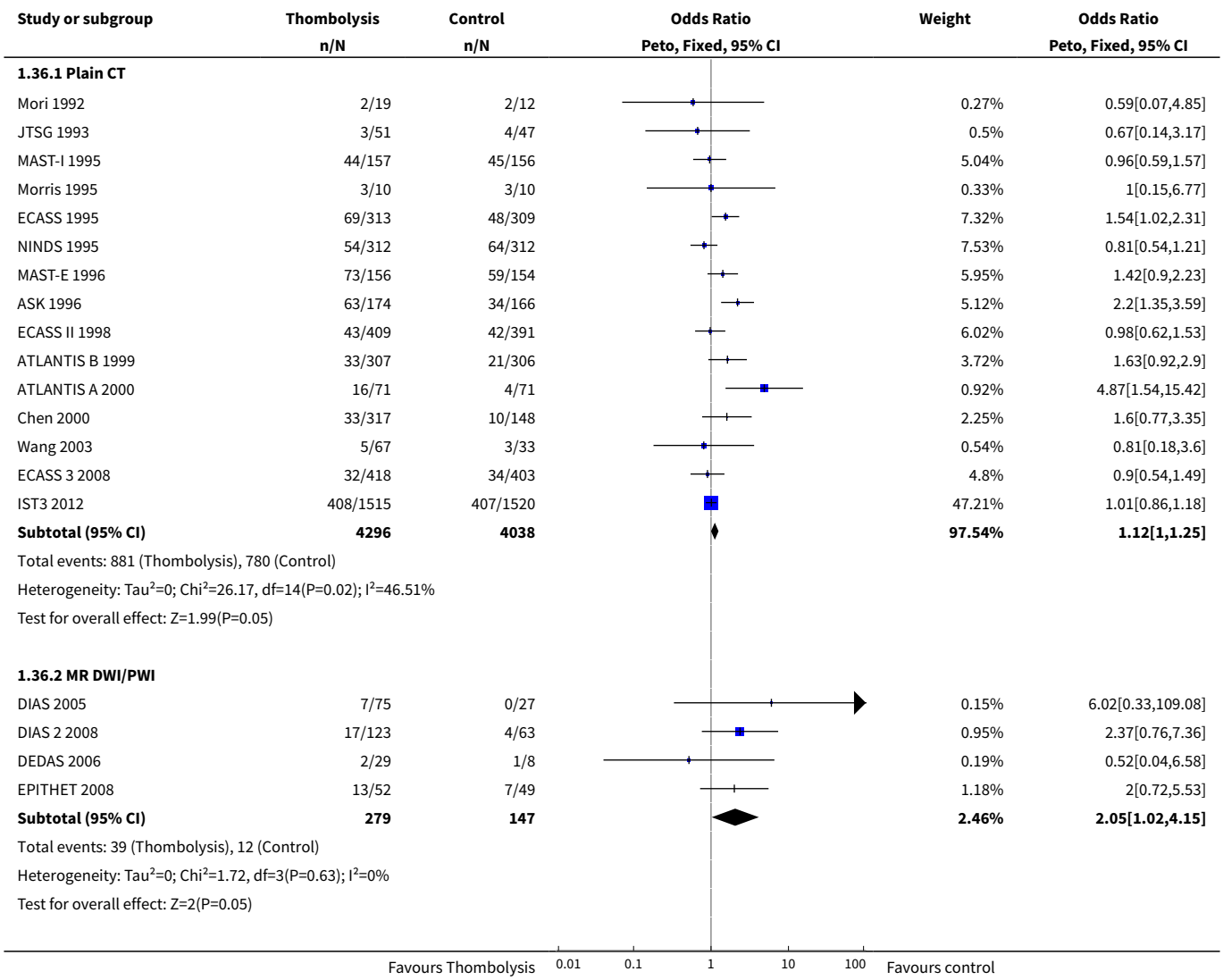
Analysis 1.35. Comparison 1 Any thrombolytic agent versus control, Outcome 35 Alive and independent (mRS 0 to 2) at end of follow-up, participants treated 3 - 6 hours, aged ≤ 80 years versus > 80 years.

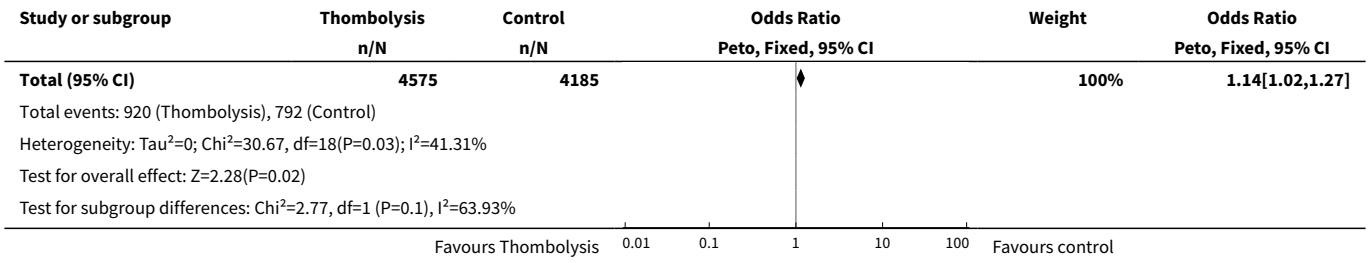
Study or subgroup	thrombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.35.1 Participants aged ≤ 80 years					
ECASS 1995	121/264	109/269		11.34%	1.24[0.88,1.75]
ECASS II 1998	180/328	147/314		13.91%	1.38[1.01,1.88]
ATLANTIS B 1999	151/284	158/286		12.28%	0.92[0.66,1.28]
ATLANTIS A 2000	6/61	12/59		1.34%	0.44[0.16,1.2]
ECASS 3 2008	278/418	248/403		16.38%	1.24[0.93,1.65]
EPITHET 2008	20/38	18/36		1.62%	1.11[0.45,2.74]
IST3 2012	298/611	313/630		26.88%	0.96[0.77,1.2]
Subtotal (95% CI)	**2004**	**1997**		**83.76%**	**1.09[0.96,1.24]**
Total events: 1054 (thrombolysis), 1005 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.91, df=6(P=0.18); I^2=32.65%					
Test for overall effect: Z=1.4(P=0.16)					
1.35.2 Participants aged > 80 years					
EPITHET 2008	2/13	2/12		0.3%	0.91[0.11,7.43]



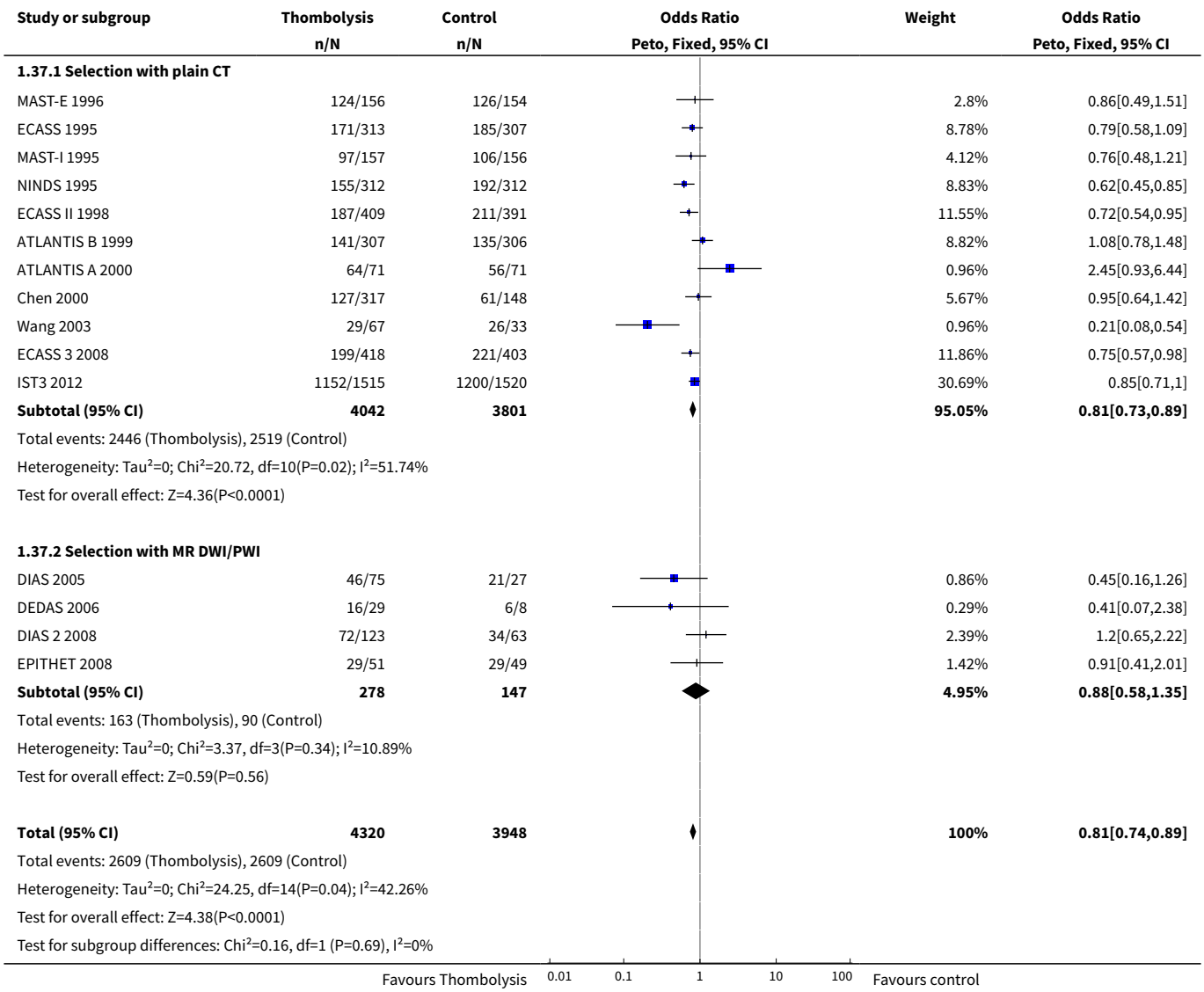


Analysis 1.36. Comparison 1 Any thrombolytic agent versus control, Outcome 36 Death: selection by MR DWI/PWI or CT.





Analysis 1.37. Comparison 1 Any thrombolytic agent versus control, Outcome 37 Death or dependency: selection with MR DWI/PWI versus plain CT.



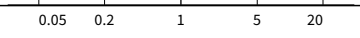
Analysis 1.38. Comparison 1 Any thrombolytic agent versus control, Outcome 38 Symptomatic intracranial haemorrhage: selection with MR DWI/PWI or CT.

Study or subgroup	Thombolysis n/N	Control n/N	Odds Ratio Peto, Fixed, 95% CI	Weight	Odds Ratio Peto, Fixed, 95% CI
1.38.1 Plain CT					
Mori 1992	2/19	1/12		1.05%	1.29[0.1,16.04]
JTSG 1993	4/51	5/47		3.5%	0.71[0.18,2.84]
Haley 1993	0/14	1/13		0.62%	0.29[0.01,7.7]
NINDS 1995	20/312	2/312		3.11%	10.62[2.46,45.82]
MAST-E 1996	33/156	4/154		5.87%	10.06[3.47,29.18]
MAST-I 1995	10/157	1/156		1.56%	10.54[1.33,83.39]
ECASS 1995	62/313	20/307		23.55%	3.54[2.08,6.03]
Morris 1995	2/10	0/10		0.66%	6.18[0.26,146.78]
ASK 1996	22/174	4/166		5.62%	5.86[1.97,17.4]
ECASS II 1998	36/409	13/391		15.75%	2.81[1.46,5.38]
ATLANTIS B 1999	21/307	4/306		5.69%	5.54[1.88,16.35]
Chen 2000	12/317	3/148		4.06%	1.9[0.53,6.84]
ATLANTIS A 2000	8/71	0/71		0.81%	19.14[1.08,338.32]
Wang 2003	1/67	0/33		0.64%	1.51[0.06,38.11]
ECASS 3 2008	10/418	1/403		1.57%	9.85[1.26,77.32]
IST3 2012	104/1515	16/1519		23.58%	6.92[4.07,11.78]
Subtotal (95% CI)	**4310**	**4048**		**97.64%**	**4.38[3.38,5.69]**
Total events: 347 (Thombolysis), 75 (Control)					
Heterogeneity: Tau^2=0; Chi^2=24.04, df=15(P=0.06); I^2=37.61%					
Test for overall effect: Z=11.1(P<0.0001)					
1.38.2 MR DWI/PWI					
DIAS 2005	9/75	0/27		0.8%	7.86[0.44,139.73]
DIAS 2 2008	5/123	0/63		0.79%	5.89[0.32,108.32]
DEDAS 2006	0/29	0/8			Not estimable
EPITHET 2008	4/52	0/49		0.77%	9.19[0.48,175.23]
Subtotal (95% CI)	**279**	**147**		**2.36%**	**7.51[1.4,40.35]**
Total events: 18 (Thombolysis), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=2(P=0.98); I^2=0%					
Test for overall effect: Z=2.35(P=0.02)					
Total (95% CI)	**4589**	**4195**		**100%**	**4.44[3.43,5.75]**
Total events: 365 (Thombolysis), 75 (Control)					
Heterogeneity: Tau^2=0; Chi^2=24.47, df=18(P=0.14); I^2=26.44%					
Test for overall effect: Z=11.32(P<0.0001)					
Test for subgroup differences: Chi^2=0.38, df=1 (P=0.54), I^2=0%					

Favours Thombolysis — Favours control

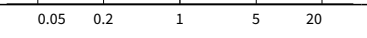
Analysis 1.39. Comparison 1 Any thrombolytic agent versus control, Outcome 39 Alive and independent (mRS 0 to 1) at end of follow-up, by plain CT ASPECTS score.

Study or subgroup	Thrombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.39.1 ASPECTS score 8 - 10					
NINDS 1995	96/201	59/205		9.57%	2.23[1.5,3.33]
ECASS II 1998	126/280	114/277		13.63%	1.17[0.84,1.63]



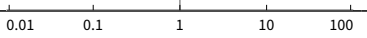
Favours control — Favours thrombolysis

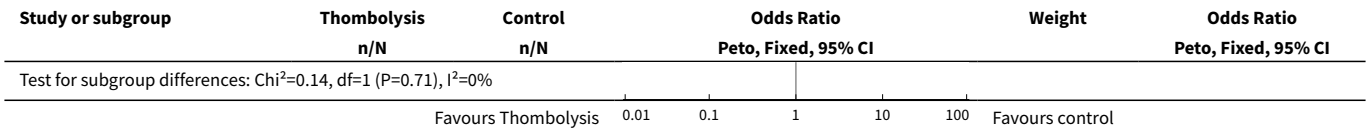
Study or subgroup	Thrombolysis n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
PROACT 2 1999	17/46	2/20		1.16%	3.65[1.16,11.54]
IST3 2012	487/1144	466/1144		55.42%	1.08[0.91,1.27]
Subtotal (95% CI)	**1671**	**1646**		**79.78%**	**1.21[1.06,1.39]**
Total events: 726 (Thrombolysis), 641 (Control)					
Heterogeneity: Tau²=0; Chi²=14.4, df=3(P=0); I²=79.17%					
Test for overall effect: Z=2.75(P=0.01)					
1.39.2 ASPECTS score 0 - 7					
NINDS 1995	33/99	22/103		4.01%	1.82[0.98,3.39]
ECASS II 1998	37/124	26/107		4.56%	1.32[0.74,2.36]
PROACT 2 1999	12/59	7/29		1.33%	0.8[0.27,2.35]
IST3 2012	63/363	62/366		10.33%	1.03[0.7,1.51]
Subtotal (95% CI)	**645**	**605**		**20.22%**	**1.2[0.91,1.58]**
Total events: 145 (Thrombolysis), 117 (Control)					
Heterogeneity: Tau²=0; Chi²=3.02, df=3(P=0.39); I²=0.71%					
Test for overall effect: Z=1.3(P=0.19)					
Total (95% CI)	**2316**	**2251**		**100%**	**1.21[1.07,1.37]**
Total events: 871 (Thrombolysis), 758 (Control)					
Heterogeneity: Tau²=0; Chi²=17.43, df=7(P=0.01); I²=59.84%					
Test for overall effect: Z=3.04(P=0)					
Test for subgroup differences: Chi²=0.01, df=1 (P=0.94), I²=0%					



Analysis 1.40. Comparison 1 Any thrombolytic agent versus control, Outcome 40 Death or dependency at the end of follow-up: intra-arterial thrombolysis versus control.

Study or subgroup	Thombolysis n/N	Control n/N	Odds Ratio Peto, Fixed, 95% CI	Weight	Odds Ratio Peto, Fixed, 95% CI
1.40.1 Intra-arterial urokinase versus control					
AUST 2005	4/8	7/8		3.54%	0.14[0.01,1.76]
MELT 2007	25/57	35/57		39.99%	0.49[0.23,1.04]
Subtotal (95% CI)	**65**	**65**		**43.52%**	**0.44[0.22,0.91]**
Total events: 29 (Thombolysis), 42 (Control)					
Heterogeneity: Tau²=0; Chi²=0.85, df=1(P=0.36); I²=0%					
Test for overall effect: Z=2.22(P=0.03)					
1.40.2 Intra-arterial pro-urokinase versus control					
PROACT 1998	18/26	11/14		9.6%	0.61[0.13,2.82]
PROACT 2 1999	73/121	44/59		46.87%	0.52[0.26,1.03]
Subtotal (95% CI)	**147**	**73**		**56.48%**	**0.53[0.28,1]**
Total events: 91 (Thombolysis), 55 (Control)					
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.84); I²=0%					
Test for overall effect: Z=1.96(P=0.05)					
Total (95% CI)	**212**	**138**		**100%**	**0.49[0.31,0.79]**
Total events: 120 (Thombolysis), 97 (Control)					
Heterogeneity: Tau²=0; Chi²=1.03, df=3(P=0.79); I²=0%					
Test for overall effect: Z=2.94(P=0)					





APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE (Ovid) 1966 to November 2013

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 recanalis$ 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 November 2013

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 recanalis$ 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

F E E D B A C K

Concomitant use of antithrombotic treatment

Summary

Category: Methodological qualities of included studies

This review (*The Cochrane Library* Issue 1,1997) states that ".. in the NINDS (1995), Mori et al 1992, and Haley et al 1993 no antithrombotic drugs were allowed within 24 hours .". However, Haley et al published that "Intravenous heparin was prohibited until at least 30 minutes after the infusion was complete .." thereby suggesting that heparin may have been given much earlier than 24 hours.

Reply

Wardlaw et al have tried to contact Haley et al but without success. Hence, they have changed the text to ".. in Haley et al (1993) a few patients received antithrombotic drugs within 24 hours ..".

Contributors

Comment by Ryan CW, April 1997
Response by Wardlaw J et al, December 1997

Feedback, 21 March 2015

Summary

Comment: We commented on this Cochrane review and the overall evidence reported for alteplase use at 3-4.5 hours after stroke (BMJ. 2015 Mar 17;350:h1075) and provide specific feedback for improving this Cochrane review.

In the Risk of bias in included studies section, it would be helpful:
1.) to include a risk of bias summary table

2.) in the paragraph on incomplete outcome data, to describe the completeness of the available data explicitly rather than stating all available data are included. Describe the risk of bias from incomplete data, including a trial-specific understanding of how prevalent or nonprevalent this risk is

3.) in the paragraph on selective reporting, to define what you mean by "strict intention-to-treat analysis". Does this mean that outcomes were assumed and assigned for all randomized patients, regardless of follow-up data availability? And if missing data was imputed, how was it done, and was it done in a similar way in each trial? Also, presenting sensitivity analyses and including an available case analysis would be useful. Regardless of how you describe your methodology for approaching intention-to-treat analysis, comment on whether the data is available or the intention-to-treat analyses were available from the trials to determine if absence of intention-to-treat analyses represents a risk of bias in the data at a trial-specific level.

4.) to add a discussion on baseline differences: What relevant factors, if any, were imbalanced between groups in each trial? This is an important risk of bias criterion not addressed in the review.

In the Results section and subsequent discussions and conclusions:
1.) While there are many analyses that can be grouped by time in many ways (0-3 hours, 0-4.5 hours, 0-6 hours, 3-6 hours, 3-4.5 hours, 4.5-6 hours), providing data for many overlapping combinations is confusing, so timeframes that do not represent clinically useful and methodologically sound groups should be dropped from the results reporting.

2.) Overall timeframes such as 0-4.5 hours and 0-6 hours are not useful for clinical decision making or overall data interpretation because:

a. Clinical practice patterns and guidelines have “chunked” practice into 0-3 hours, 3-4.5 hours, and 4.5-6 hours for practical implementation.

b. The data in the existing Cochrane review have such different results in subgroup analyses for 0-3 hours and for 3-6 hours that lumping these two together for an overall analysis does not provide a summary statistic that is representative of a clinically representative grouping of patients. The 'average' of these two groupings does not represent the 'whole'.

c. If data for 3-4.5 hours and 4.5-6 hours could be separated this may be more clear than analyses for 3-6 hours.

3.) Addressing the impact of risk of bias assessments could be important for results interpretation and discussion.

The changes above could be applied relatively quickly and are important considering the Cochrane review could be expected to be the most valid, thorough and current systematic review for this subject.

Meanwhile, if Cochrane reviewers could obtain the full data, address population subgroupings considered most clinically relevant (age < 80 years vs. age > 80 years, timeframes 0-3 hours vs. 3-4.5 hours), and provide an updated individual patient data meta-analysis, it would immensely help policy-makers view this in full detail. A protocol for such an analysis being shared a priori with an opportunity for clinicians, researchers, and content domain experts to comment on which subgroupings are most clinically relevant and which approaches to the data interpretation and analysis are most likely to be informative or potentially introducing a risk of bias would allow for a meta-analysis with wider acceptance and greater confidence in its results.

Reply

We thank Brian Alper and colleagues for their interest in our review, and for their comments. Our responses (in bold) are listed below point by point. Many of the points raised cannot be answered by the tabular data of the review (for example the effects in different time splits). However, these were answered by the Stroke Thrombolysis Trialists' Collaboration (STTC) publication in the Lancet in 2014, which is referenced in the review.

Comment: We commented on this Cochrane review and the overall evidence reported for alteplase use at 3-4.5 hours after stroke (BMJ 2015 Mar 17;350:h1075) and provide specific feedback for improving this Cochrane review.

Response: Thank you for your interest in the review and for taking the time to submit this critique.

In the Risk of bias in included studies section, it would be helpful:

1) to include a risk of bias summary table.

Response: Thank you. We have provided 'Risk of bias' tables for the trials included since the last update, and plan to extend to all trials in the next revision. However, we clearly state the major issues related to bias in the text and state in the Methods in 'Assessment of risk of bias':

"We assessed risk of bias as specified in the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (March 2011), Chapter 8 (Higgins 2011). We assessed whether the method of randomisation would allow allocation concealment, the adequacy of efforts to blind treatment administration and outcome assessment. For each included trial we collected information about:

- *the method of randomisation (including information on allocation concealment);*
- *blinding of treatment administration;*
- *blinding of outcome assessment; and*
- *whether an intention-to-treat analysis was done, or could possibly be done.*

We provide detailed 'Risk of bias' tables for the trial included since the last update."

2) to describe, in the paragraph on incomplete outcome data, the completeness of the available data explicitly rather than stating all available data are included. Describe the risk of bias from incomplete data, including a trial-specific understanding of how prevalent or nonprevalent this risk is.

Response: We do report the following about incomplete outcome data:

"Incomplete outcome data (attrition bias)

All available data are included. Data on six participants were missing from the ATLANTIS B 1999 trial publication and details have not been forthcoming from the investigators, and we have not yet received data on 46 participants from the Chinese UK Trial (Chen 2000) (these participants were randomised after the trial's six-hour time limit and have not yet been supplied). More information is available for some trials than for others, either because the trial collaborators have published very actively on various aspects of their trial, or because in some cases further information is available from other sources (for example, reports on NINDS 1995 appear on the US Food and Drug Administration (FDA) website as part of the licence application process). The more frequent reporting or greater completeness of the data for some trials is merely a reflection that more information is available for those trials, and not intended to over- or under-emphasise the actual results or quality of any particular trial (or trials) compared with others for which there is less detailed information available.

There was more detail about each trial in the text in earlier versions and in drafts of the present version. However, space constraints imposed by the Cochrane Database of Systematic Reviews (CDSR), the large volume of important information that now has to be included, and the historical nature of some of the trials (which, note, are also relatively small), meant that these details have not been retained in the text. Note we state clearly in Methods, 'Dealing with missing data':

"We contacted trial investigators to obtain all unpublished missing data where possible. Where data were still missing or had not been collected in the original trial, then that trial did not contribute to the relevant outcome. We clarified missing or unclear data with the principal investigator. The outcomes in two studies were very clearly described in the original texts and verification with the principal investigators was not necessary (Haley 1993; Morris 1995)."

Also see Methods 'Assessment of reporting biases':

"We have endeavoured to include data from all trials on all prespecified outcomes, obtained from secondary publications or the trial investigators if unpublished. We assessed the likelihood of missing trials using a funnel plot."

The risk of bias from incomplete data is dependent on whether or not the trials used blinded outcome assessment. We will therefore also refer to Results, from the five sections on five different important sources of bias:

"Blinding (performance bias and detection bias)

Five trials were single-blind without a placebo (AUST 2005; MAST-I 1995; MELT 2007; PROACT 2 1999; Wang 2003). In one trial (IST3 2012) the first 276 participants were treated in the double-blinded phase of the trial and all 2759 remaining participants were included into the open phase of the trial. All participants in the study, irrespective of study phase, were blindly assessed by postal mail or telephone by a blinded and trained observer. In PROACT 2 1999, the control group underwent catheter placement but received no infusion. All the rest were double-blind placebo-controlled trials. However, it should also be noted that thrombolysis, due to its effects on the coagulation system at high doses, can be difficult to blind completely due to the obvious signs of bleeding (prolonged bleeding at venepuncture sites, easy bruising, gingival or conjunctival haemorrhages, etc). Thus, provision of an identical-appearing placebo (in the syringe) may not fully blind investigators to treatment allocation. Furthermore, as thrombolytic agents are proteins, they froth when shaken in solution with water or saline, rather like egg white mixed with water and shaken. Normal saline is therefore not an identical-looking placebo for a thrombolytic agent. Thus, in addition to the possibilities

for failure of treatment allocation concealment inherent in the randomisation methods used as outlined above, it is possible that treatment allocation could be guessed accurately by the physicians caring for the participant in the acute phase because of these biological effects. Accordingly, methods for ensuring complete blinding of treatment allocation at late follow-up are crucial. Only one study (MAST-I 1995) used central telephone follow-up by a blinded trained observer. Although seven other trials specified that follow-up was to be by a physician not involved in the acute care of the participant, it is uncertain how completely this was achieved in practice. Other trials either did not specify who should do the follow-up, or did not make it mandatory that follow-up was by an independent physician, so in either case follow-up may have been carried out by the acute phase physician who could have been influenced by their knowledge of events in the acute phase."

Also, the risk of bias from incomplete data is dependent on other sources of bias. We have, therefore, copied from the three other sections on different important sources of bias in the Results section, here for avoidance of doubt:

"Allocation (selection bias)

Among the included studies 14 (52%) fulfilled criteria for high grade concealment. The concealment has successively improved over time with the development and utilisation of new randomisation methods, such as the use of a centralised computerised method with interactive interface for randomisation over the telephone or Internet.

- *Twelve trials used central telephone or Internet randomisation (ASK 1996; AUST 2005; DEDAS 2006; DIAS 2005; DIAS 2 2008; ECASS 3 2008; IST3 2012; MAST-E 1996; MAST-I 1995; MELT 2007; PROACT 1998; PROACT 2 1999). In five studies (AUST 2005; IST3 2012, MAST-I 1995; MELT 2007; PROACT 2 1999), the allocated treatment was then given unblinded without a placebo. In one of the studies (IST3 2012) with the exception of 276 participants treated in the double-blinded phase of the trial, the remaining participants (2759) were treated unblinded without placebo. In four other studies (ASK 1996; ECASS 3 2008; MAST-E 1996; PROACT 1998) sealed prepacks of thrombolytic drug or identical-appearing placebo were given according to the randomisation instructions.*
- *In three trials randomisation was at the participating hospital by selection of a sealed, sequentially-numbered, prepack (of active drug or identical appearing placebo) followed within two hours by a telephone call to the Central Trial Co-ordinating Office to notify them of the participant and the number of the drug pack (ATLANTIS A 2000; ATLANTIS B 1999; NINDS 1995). In one study (NINDS 1995), the randomisation system, set up in an effort to reduce delays to treatment, led to 'out of order' trial treatment allocations in between 13 and 31 participants, which affected every subsequent participant until the error was detected, and led to participants appearing to cross between treatment allocations (more moved from rt-PA to placebo than the other way round). Also in the interests of reducing delays to trial treatment administration, there were some participants who ultimately were not entered into the study after the pharmacy had prepared the trial pack (and therefore some discarded trial packs). Details of the randomisation are given at www.fda.gov/cber/products/altegen061896.htm; see Clinical Review 2, page 11-12 and 18-19.*
- *In three trials, randomisation was by selection of a sequentially numbered, sealed drug prepack at the participating centre provided by the sponsor from a randomisation schedule drawn up centrally (ECASS 1995; ECASS II 1998; EPITHET 2008).*

Of the remaining trials:

- *five trials used sealed drug prepacks of active drug or identical-appearing placebo (Abe 1981; Atarashi 1985; JTSG 1993; Mori 1992; Ohtomo 1985);*
- *one used sealed envelopes (Haley 1993);*
- *one used sealed drug prepacks of active drug or normal saline (as placebo) (Chen 2000);*
- *the method was not stated in two (Morris 1995; Wang 2003).*

Please note that, therefore, only two of the rt-PA trials (ECASS 3 2008: IST3 2012) recorded the participant details centrally over the telephone or Internet prior to starting trial treatment. In one of these trials (IST3 2012) a minimisation algorithm was used to balance the study arms for key prognostic variables like stroke severity before randomisation. Several later studies have made use of modern randomisation techniques and entering key prognostic variables into the IT system before randomisation, which allows balancing of the study arms - as has been introduced in one trial (IST3 2012).

Selective reporting (reporting bias)

We have avoided, as far as possible, any reporting bias by obtaining original data from the trial investigators where these have not been published. Only the intention-to-treat results are included here. In any trials where there have been exclusions, these were made prior to the breaking of the randomisation code. A strict intention-to-treat analysis was used in 18 studies (ASK 1996; ATLANTIS A 2000; ATLANTIS B 1999; AUST 2005; DEDAS 2006; DIAS 2005; DIAS 2 2008; ECASS 1995; ECASS II 1998; ECASS 3 2008; EPITHET 2008; IST3 2012; MAST-E 1996; MAST-I 1995; MELT 2007; PROACT 1998; PROACT 2 1999; Wang 2003), but not in any of the earlier trials. The administrative problems with randomisation in one study (NINDS 1995) led the FDA reviewer to describe the primary analysis as an 'on-treatment analysis'. However, the primary analysis was undertaken without excluding any participants entered into the trial and was, therefore, an intention-to-treat analysis (www.fda.gov/cber/products/altegen061896.htm; see Clinical Review 2, page 20). For the earlier trials, with additional information from the principal investigators if necessary, we have attempted to find a final outcome for all randomised participants, rather than simply relying on the published data from which some randomised participants may have been excluded. Note that one trial (ECASS 1995) was published as intention-to-treat and as a 'target population' after about 20% of the randomised participants had been excluded, but only the intention-to-treat data have been included here.

Other potential sources of bias

Randomisation in two trials, ASK 1996 (in the over-three-hour group) and MAST-E 1996, was stopped on the advice of their respective data monitoring committees after only about half of the originally intended number of participants had been randomised. One study (MAST-I 1995) was suspended by its steering committee (in view of the stopping of MAST-E 1996 and ASK 1996) to examine its interim results after randomising about one third of its originally intended number. Another study (MELT 2007) was discontinued on the advice of its data monitoring committee when rt-PA was licensed in Japan in 2005. Another study (AUST 2005) was discontinued on the basis of very slow recruitment after 24 participants of a planned sample of 200 had been included. Four studies (ECASS 1995; ECASS II 1998; NINDS 1995; PROACT 2 1999) all reached their planned targets. One study (PROACT 1998) was stopped after completing two of its planned three dosage arms by the pharmaceutical provider. Another study (ATLANTIS A 2000) was stopped on publication of the NINDS 1995 trial, and continued in modified form as ATLANTIS B 1999, which in turn stopped in 1998 following a 'futility analysis' prompted by results from the ECASS II 1998 study. Examination of funnel plots for the main outcomes showed these to be symmetrical and therefore provided little evidence of publication bias."

3) to define, in the paragraph on selective reporting, what you mean by "strict intention-to-treat analysis". Does this mean that outcomes were assumed and assigned for all randomised patients, regardless of follow-up data availability? And if missing data was imputed, how was it done, and was it done in a similar way in each trial? Also, presenting sensitivity analyses and including an available case analysis would be useful. Regardless of how you describe your methodology for approaching intention-to-treat analysis, comment on whether the data is available or the intention-to-treat analyses were available from the trials to determine if absence of intention-to-treat analyses represents a risk of bias in the data at a trial-specific level.

Response: 'Intention to treat' means analysed by treatment group to which the subject was assigned at randomisation, rather than by the treatment that they actually got. This is a standard term. All analyses were done as intention-to-treat analyses, and there were no assumptions, imputations or other fiddling with the data. The data are as published in the individual trials in almost all cases and can be extracted should you wish to repeat these analyses yourselves. In a few trials, additional unpublished data were sought and included but these were mostly for secondary outcomes. Also see above.

4) to add a discussion on baseline differences: What relevant factors, if any, were imbalanced between groups in each trial? This is an important risk of bias criterion not addressed in the review.

Response: A detailed discussion on baseline imbalance was included in previous versions of this review over the last 15 years but has mostly been removed from the current version due mainly to space constraints and because there has been an extensive debate and reanalysis (e.g. of the NINDS trial) all of which is referenced, plus the STTC individual patient data meta-analysis (Lancet 2014, see references), all of which overcome concerns regarding baseline imbalance. Also see sections on bias from Results copied above.

In the Results section and subsequent discussions and conclusions:

1) While there are many analyses that can be grouped by time in many ways (0-3 hours, 0-4.5 hours, 0-6 hours, 3-6 hours, 3-4.5 hours, 4.5-6 hours), providing data for many overlapping combinations is confusing, so timeframes that do not represent clinically useful and methodologically sound groups should be dropped from the results reporting.

Response: With respect, a) many would disagree on what constitutes a clinically meaningful time window, and b) tabular data on 3-4.5 or 4.5-6 hours have not been published from most trials. Only ECASS-3 examined 3-4.5 hours and IST-3 provided 3-4.5 hour data in a prespecified subgroup analysis. There is substantial interest in 0-3 hours and 3-6 hours and these times are available. Therefore we provide these times and refer the reader to the STTC analysis (Lancet 2014). The several time subgroups are clearly labelled and their presence explained in the text. The separate analyses are retained for trials that randomised in both 0-3 and 3-6 hour time windows to deal with the difference in stroke severity seen in early vs later presenting patients, which was not otherwise possible with tabular data.

2) Overall timeframes such as 0-4.5 hours and 0-6 hours are not useful for clinical decision making or overall data interpretation because:

a. Clinical practice patterns and guidelines have “chunked” practice into 0-3 hours, 3-4.5 hours, and 4.5-6 hours for practical implementation.

b. The data in the existing Cochrane review have such different results in subgroup analyses for 0-3 hours and for 3-6 hours that lumping these two together for an overall analysis does not provide a summary statistic that is representative of a clinically representative grouping of patients. The “average” of these two groupings does not represent the “whole”.

c. If data for 3-4.5 hours and 4.5-6 hours could be separated this may be more clear than analyses for 3-6 hours.

Response: See above. As only 2 trials provide 3-4.5 hr data, there is little point in creating separate tables, because the sample would be too small. The STTC analysis addresses this issue adequately, clearly showing that the latest time window for alteplase (rt-PA) is around 5 hrs or just after. Please note a methodological point however: the lack of patients randomised beyond six hours means that it is not possible to determine the very latest time window at present – for now we can only be confident of some benefit out to 5 hours – a larger sample, as is seen where all thrombolytic drugs (10,000 patients) are considered, suggests a definite benefit

out to six hours. Confirmation of this point will be possible with the results of more later time window trials. Note that the recent positive (small) thrombectomy trials had time windows out to 8 hours.

3) Addressing the impact of risk of bias assessments could be important for results interpretation and discussion.

Response: We have above copied from the five sections on different important sources of bias, from Results. For avoidance of doubt, please see also the three sections on these points in the Discussion:

"Overall completeness and applicability of evidence

The trials included in this review are small in comparison with the thrombolytic therapy in myocardial infarction trials. Nonetheless, this version of the review, with the addition of IST3 2012, includes a wider range of participants, with many more aged over 80 years, than previous versions. This is an effect of the principal methodology of IST3 2012 with the application of the uncertainty principle, which states that when there is a clear indication for treatment the person should be treated, and when there clearly is a contraindicated the person should not be treated; only where the tested treatment is promising but unproven could the participant be randomised. This approach provides the chance to test wider treatment criteria. There are substantially more data with the inclusion of 3035 participants from IST3 2012. However, not all trials contributed to all analyses, some analyses only include five or so trials and there were imbalances in stroke severity and age between treatment groups in some earlier trials. There remains significant heterogeneity for some outcomes and lack of a complete picture of the sources of heterogeneity, meaning that there is scope for more trials. This is particularly the case for mild strokes. Although there is a lack of information on concomitant aspirin usage, it seems fairly clear from MAST-I 1995 and the non-random comparisons in Analysis 1.14 that aspirin (or other antithrombotic drugs) given at the same time as thrombolysis is hazardous. The adverse effect of aspirin together with rt-PA was confirmed in one recent trial that stopped prematurely due to excess bleeding with aspirin and rt-PA combined (Zinkstok 2008). We have not been able to identify clear reasons why some people do poorly with thrombolysis. For example, the absence of any apparent time dependence of SICH with thrombolysis suggests that some other non-time-dependent factors may increase haemorrhage risk - i.e., not the presence of acute ischaemic change or other time-dependent factors. In contrast, the benefit of thrombolysis declines with time, fewer patients being alive and independent the later the treatment. The independent data meta-analysis of all rt-PA trials may be better able to identify factors influencing hazard.

The time window beyond which there is unlikely to be any benefit (or too much hazard) with thrombolytic therapy is unclear. The modifiers of the adverse effects of thrombolytic mode of action remain undetermined. There is a clear time dependency, with fewer participants treated within three hours of stroke being dead or dependent, than participants treated between three and six hours, but the latest time window remains undetermined. Other trials that tested other thrombolytic regimens beyond six hours suggest that the benefit may extend to nine hours or even longer in selected people. Although these trials were themselves not positive, when combined the overall result suggests that thrombolysis reduces death or dependency even at these later times. Thus, the time window for benefit probably extends to, and even beyond, six hours in selected people. However, this should not encourage complacency about the need for speedy treatment in ischaemic stroke. It simply underlines the need for more data so as to be able to provide individually-tailored treatment accounting for age, sex, stroke severity, prior aspirin use, brain scan appearances, etc., to name but a few factors in addition to time, which are likely to affect thrombolysis effect.

There is little information on which thrombolytic drug might have most benefit and least hazard, and there is little information on which dosage of drug has least hazard and most benefit (Wardlaw 2013). Direct randomised comparisons would be required (Dundar 2003). The Chinese UK trial (Chen 2000) had two doses of urokinase, but was underpowered to detect any difference between them. Similarly, the DEDAS 2006, DIAS 2005, and DIAS 2 2008 trials were together underpowered to detect a difference between doses of desmoteplase. Note that further details on direct randomised comparisons of drug or dose are included in a separate Cochrane Review (Wardlaw 2013), for which there are few additional data since its original publication.

There is limited information about the effect of thrombolysis on survival in a longer time frame, as most of the trials (all of the recent rt-PA trials) performed the follow-up at three months. NINDS 1995 published data on functional outcome at six months and one year which indicate that the effect of rt-PA was sustained beyond three months. IST3 2012 published data on functional outcome and death at 18 months which also indicate long-term benefits, but there are few other data on whether the benefit of thrombolysis is sustained (or even increases) at one year. This information is important for understanding the impact of thrombolytic treatment on health economics.

It is difficult to assess the cost effectiveness of thrombolytic treatment. A review for the UK National Health Service Health Technology Assessment (HTA) Programme on the cost effectiveness of thrombolytic treatment for acute ischaemic stroke needs to be updated (Sandercock 2002). One trial has a prospective substudy ongoing for the measured and modelled evaluation of cost effectiveness (IST3 2012).

Quality of the evidence

The overall quality of evidence, particularly for the drug with the majority of data, rt-PA, is good. The concerns about quality in earlier trials are largely overcome. The recent trials had good allocation concealment, central telephone randomisation, central blinded follow-up, and very few losses to follow-up.

Potential biases in the review process

This review is the result of an ongoing process involving the collaborative effort of many researchers worldwide and the principal investigators of many of the thrombolysis trials. At present, this review represents all of the evidence from the randomised controlled studies on the effects

of thrombolytic therapy on acute ischaemic stroke. Comparisons of trials using different thrombolytic drugs should be treated with caution as these comparisons are indirect; available data on direct comparisons are presented in the companion review (Wardlaw 2013). We have tried to include all available tabular data and have checked the accuracy of it rigorously. We have tried not to miss any relevant completed trials. We can only apologise if we have overlooked some available data on an outcome in an included trial or have overlooked a trial completely."

The changes above could be applied relatively quickly and are important considering the Cochrane review could be expected to be the most valid, thorough and current systematic review for this subject.

Response: Thank you but please take note of the above points, particularly that of space constraints. A large amount of text had to be culled from the present version at a late stage. Perhaps the CDSR could consider increasing their space – an electronic publishing medium should not impose text space constraints. The information you refer to is not 'missing' from the review – information on bias is given in the text and the published trial reports do not contain tabular data on the specific time window you request. Earlier versions provide detailed descriptions and discussion of baseline imbalance. However these issues concern only two trials (NINDS and ECASS III) of only about 1400 patients (of 7000 patients treated with alteplase or 10,000 patients treated with any thrombolytic drug). Disputes over this have already been settled, and the STTC individual patient data meta-analysis has already overcome concerns over this.

Meanwhile, if the Cochrane reviewers could obtain the full data, address population subgroupings considered most clinically relevant (age < 80 years vs. age > 80 years, timeframes 0-3 hours vs. 3-4.5 hours), and provide an updated individual patient data meta-analysis, it would immensely help policy-makers view this in full detail. A protocol for such an analysis being shared a priori with an opportunity for clinicians, researchers, and content domain experts to comment on which subgroupings are most clinically relevant and which approaches to the data interpretation and analysis are most likely to be informative or potentially introducing a risk of bias would allow for a meta-analysis with wider acceptance and greater confidence in its results.

Response: The STTC has already done exactly what you suggest and published both the protocol and the results in 2014. For the Cochrane review, all available data are in the data tables, and the primary and secondary trials publications are all listed in the review so that interested readers can go and replicate this 25 years' worth of analysis should they wish.

Contributors

Commentors: Brian S Alper, Meghan Malone-Moses, James S McLellan, Kameshwar Prasad, Eric Manheimer

Responders: Joanna Wardlaw, Eivind Berge

Feedback, 11 November 2015

Summary

We previously provided feedback (dated March 21, 2015) and your many responses to numerous concerns did not address a highly specific concern regarding the baseline difference in history of prior stroke in ECASS III, and how adjusting for this may negate any evidence of efficacy for alteplase 3 to 4.5 hours after stroke onset.

The ECASS III trial (Hacke et al. New England Journal of Medicine 2008 25;359(13):1317-29) is the only trial supporting efficacy of alteplase 3 to 4.5 hours after stroke. A potentially serious risk of bias in ECASS III was the baseline difference in history of prior stroke, a finding that was present in 7.7% of alteplase patients and 14.1% of placebo patients.

Detailed discussions on baseline imbalances that were included in previous versions of this review (2000, 2003, or 2009) do not adequately cover the baseline difference in history of prior stroke in ECASS III and its specific influence on conclusions regarding efficacy 3 to 4.5 hours after stroke, either in ECASS III alone or in analysis of all available data for this timeframe.

This baseline difference was erroneously reported in ECASS III as non-significant in the original trial report in 2008 and not corrected until 2011, so none of this should be considered "settled" or referred to historically. In the 2008 ECASS III report, the adjusted analyses to show the primary outcome was robust when adjusting for baseline differences did not adjust for the history of prior stroke.
The P value for this baseline difference in history of stroke, a potentially confounding variable, was corrected online in 2011 (from 0.03 to 0.003) without a correction notice, and this is only known based on a letter published in another journal in 2012 (Shy. Journal of Emergency Medicine 2014;46(3):385-6. Epub 2012 November 8). This letter also reported a reanalysis of ECASS III based on available summary data and limited to the 89% of patients without a prior stroke, which found no significant effect on the primary outcome.

Thus, this specific key baseline difference appears to be the primary contributor to the "statistically significant benefit" reported in ECASS III and conclusions of efficacy derived from this data or any other data should require substantial transparency and scrutiny to be accepted.

The ECASS III trial data is reported to be available at clinicalstudydatarequest.com and a reanalysis using the original data could be conducted independently. Until such reanalysis is done, it is most prudent to acknowledge this specific risk of bias, recognize its potential effect on the overall body of evidence specific to use of alteplase 3 to 4.5 hours after stroke, and not make conclusions about alteplase use 3 to 4.5 hours after stroke that extrapolate from data outside this timeframe or analyses that have not accounted for such risk of bias.

Reply

We thank Dr Alpers and colleagues for their continuing interest in the review of thrombolysis in acute ischaemic stroke. We are sorry that our responses did not address one highly specific concern.

To summarise, in ECASS 3, there was a difference in history of stroke (7.7% in the patients allocated to alteplase and 14.1% in the patients allocated to placebo). You are concerned that this difference in baseline characteristic is enough to account for the apparent benefit of rt-PA on mRS 0 to 1 at 90 days that was seen in ECASS 3, which only randomised patients between 3 to 4.5 hours after stroke. You cite a letter by Shy published in the Journal of Emergency Medicine 2014 in support of this concern. Shy refers to an adjusted analysis done by Bluhmki et al [1] restricted to the 89% of patients without a prior stroke in ECASS 3, which produced an odds ratio for the effect of rt-PA on mRS 0 to 1 of 1.19, 95% CI 0.89 to 1.59. You interpret this to mean that there is no benefit of rt-PA within the 3 to 4.5 hour time window.

We believe that the loss of significance when analysis is restricted to 89% of the data is more likely due to the diminished sample. Bluhmki et al [1] also performed a fully adjusted analysis including prior stroke, and also reported several additional outcomes and subgroup analyses beyond those provided in the original NEJM primary report [2]. In the fully adjusted model of the effect of rt-PA on mRS 0 to 1 at 90 days, Bluhmki et al [1] adjusted for NIHSS, age, weight, onset to treatment time, diastolic and systolic blood pressure, dose in mg/kg body weight, smoking, previous stroke, previous diabetes, atrial fibrillation, hypertension, previous use of antithrombotic drugs, and sex, giving an OR for mRS 0 to 1 at 90 days after stroke of 1.43 (95% CI 1.02, 2.00, P value = 0.040), which was no different to the OR in the model that included about half of those variables but not prior stroke (OR 1.42, 95% CI 1.02-1.98, P value = 0.037) and the analysis that was completely unadjusted (OR 1.34, 95% CI 1.02-1.76, P value = 0.038): see Figure 3 in 1. This would suggest that the effect of prior stroke is unlikely to be sufficient to negate the positive result of ECASS 3 on mRS 0 to 1.

We note two further points.

1. None of the trials were especially large. As we explain in the review, a consequence is that several trials go from positive to neutral, or neutral to positive, simply by switching between mRS 0 to 1 and mRS 0 to 2, or between mRS 3 to 6 and mRS 2 to 6 as the outcome. Figures 1.9, 1.10, 1.12, 1.13, etc, explore this effect in the Review and it is described in the Results and discussed in detail in the Discussion. This illustrates that the data should be viewed in totality rather than focusing too closely on individual trials, which of course is the purpose of Cochrane reviews.
2. You are concerned that the imbalance in ECASS 3 is important because ECASS 3 was the only trial that randomised in the 3 to 4.5 hour time window. However, several other trials also randomised in that time window although not exclusively. Unfortunately, as explained in a previous response, not enough of those trials published tabular data on the 3 to 4.5 hour window to make a tabular meta-analysis feasible, therefore we were not able to provide the 3 to 4.5 hour time window separately. However, as stated in the Review, there is now an individual patient data (IPD) meta-analysis which includes ECASS 3. This IPD, performed by independent statisticians, has published a very detailed analysis of the effect of rt-PA by time, with adjustments, and clearly showed that there is benefit for rt-PA between 3 and 4.5 hours after stroke [3], indeed up to between 4.5 and 5 hours after stroke, when considering all the data.

The Cochrane Review has several sections on risk of bias focusing on the main messages that apply to multiple trials. For example, about half the trials had various baseline imbalances, which were inevitable as they did not use central randomisation with minimisation, and some were of similar size or worse than the prior stroke imbalance in ECASS 3 (like those in NINDS). We believe that these major messages are more relevant than to focus on only one trial. Indeed, Cochrane editorial policy means that the limited space precludes providing very detailed descriptions of all variables in all trials.

References

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2. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. New England Journal of Medicine 2008;359:1317-29.
3. Emberson J, Lees KR, Lyden P et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929-35.

Contributors

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WHAT'S NEW

Date	Event	Description
5 January 2016	Feedback has been incorporated	See Feedback 3

HISTORY

Protocol first published: Issue 1, 1995
Review first published: Issue 1, 1995

Date	Event	Description
12 May 2015	Feedback has been incorporated	See Feedback 2
2 April 2014	New search has been performed	We have updated the searches to November 2013 with further handsearch to March 2014. The IST-3 study was the only new, completed trial since the previous update of the review in 2009. The IST-3 trial adds 3035 new participants, increasing the total number of participants to 10,187, of which the rt-PA-data increased by 43%. We have added new information from previously published trials and several new analyses of new and existing outcomes.
2 April 2014	New citation required and conclusions have changed	Substantially more information is now available on essential outcomes in subgroups of patients, e.g. by age, stroke severity, time to treatment and essential outcomes like early and late case fatality. Markers of risk for early intracerebral haemorrhage are still unidentified.
26 June 2008	Amended	Converted to new review format.
14 March 2003	New search has been performed	Additional data are included from rt-PA trials broken into under three and three to six-hour time windows. Information about the organisation of the NINDS trial randomisation method and resulting problems have come to light. A new trial from China of intravenous urokinase within six hours is included. A plain language summary has been added.

CONTRIBUTIONS OF AUTHORS

Four review authors contributed to the collection of data in previous versions, including non-English language publication literature searching. Dr Eivind Berge undertook further detailed literature searching for the 2003 update. Both Dr Veronica Murray and Prof Joanna Wardlaw reviewed all new trials since 2003 and extracted, verified and entered new data for the 2009 update. Dr Veronica Murray also cross-checked all previously extracted data. Both Prof Joanna Wardlaw and Dr Veronica Murray checked additional publications since 2003 of trials already included in the 2003 version for additional new information. All review authors also contributed to interpretation of the data. Prof Joanna Wardlaw drafted the review and the other review authors contributed to the critical revision of that review and final approval of the version to be published.

DECLARATIONS OF INTEREST

The Division of Clinical Neurosciences at the University of Edinburgh had a collaborative project with Boehringer Ingelheim (UK) to establish a research magnetic resonance scanner, through the UK Research Councils Joint Research Equipment Initiative in 1997. For this, the Division received a grant from Boehringer Ingelheim, manufacturers of rt-PA in Europe, towards the purchase of the scanner. Further details of competing interests are listed on the Division's web site (www.dcn.ed.ac.uk).

The Division of Clinical Neurosciences at the University of Edinburgh are co-ordinating the Third International Stroke Trial (IST3 2012) of intravenous tissue Plasminogen Activator within six hours of acute ischaemic stroke. Prof Joanna Wardlaw is the Imaging Principal

Investigator of this trial, Dr Veronica Murray is the Swedish National Co-ordinator and Dr Eivind Berge is the Norwegian National Co-ordinator for IST-3. The start-up phase was funded by the UK Stroke Association and PPP Foundation, with a limited supply of drug and placebo for the first part of the start-up phase from Boehringer Ingelheim; the main trial is funded by the UK Medical Research Council.

Prof Joanna Wardlaw received payment from Boehringer Ingelheim for reading scans for ECASS 3 on a cost-per-scan basis up to 2008. She was/is on the Steering Committees of MAST-I 1995, IST3 2012, and contributed to the design of ECASS 3 2008 (first Steering Committee meeting and design of scan reading). Boehringer Ingelheim applied for an extension to the licence for rt-PA from three to 4.5 hours on the basis of the ECASS 3 2008 result and supporting data, such as individual patient data analyses and the Cochrane review.

The review was assembled, analysed and reported independent of any sponsor or pharmaceutical company.

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Internal sources

- Department of Clinical Neurosciences, University of Edinburgh, Scotland, UK.

External sources

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  Grant to help update the review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None in principle. The original protocol was written in 1992, since when Cochrane Reviews have become more complex, data analyses have been refined and substantially more data have become available for this review. Notwithstanding, the basic principles of this review are unchanged from the original protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

*Thrombolytic Therapy [adverse effects]; Brain Ischemia [drug therapy]; Drug Administration Schedule; Fibrinolytic Agents [adverse effects] [*therapeutic use]; Intracranial Hemorrhages [chemically induced]; Randomized Controlled Trials as Topic; Stroke [*drug therapy] [etiology] [mortality]; Time-to-Treatment; Tissue Plasminogen Activator [adverse effects] [therapeutic use]

MeSH check words

Humans