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[Intervention Review]

Anticoagulants for acute ischaemic stroke

Peter AG Sandercock[1], Carl Counsell[2], Edward J Kane[3]

[1]Centre for Clinical Brain Sciences (CCBS), University of Edinburgh, Edinburgh, UK. [2]Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK. [3]University of Edinburgh, Edinburgh, UK

Contact address: Peter AG Sandercock, Centre for Clinical Brain Sciences (CCBS), University of Edinburgh, The Chancellor's Building, 49 Little France Crescent, Edinburgh, EH16 4SB, UK. peter.sandercock@ed.ac.uk.

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ABSTRACT

Background

Most ischaemic strokes are caused by a blood clot blocking an artery in the brain. Clot prevention with anticoagulants might improve outcomes if bleeding risks are low. This is an update of a Cochrane review first published in 1995, with recent updates in 2004 and 2008.

Objectives

To assess the effectiveness and safety of early anticoagulation (within the first 14 days of onset) in people with acute presumed or confirmed ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (June 2014), the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), the Database of Reviews of Effects (DARE) and the Health Technology Assessment Database (HTA) (*The Cochrane Library* 2014 Issue 6), MEDLINE (2008 to June 2014) and EMBASE (2008 to June 2014). In addition, we searched ongoing trials registries and reference lists of relevant papers. For previous versions of this review, we searched the register of the Antithrombotic Trialists' (ATT) Collaboration, consulted MedStrategy (1995), and contacted relevant drug companies.

Selection criteria

Randomised trials comparing early anticoagulant therapy (started within two weeks of stroke onset) with control in people with acute presumed or confirmed ischaemic stroke.

Data collection and analysis

Two review authors independently selected trials for inclusion, assessed trial quality, and extracted the data.

Main results

We included 24 trials involving 23,748 participants. The quality of the trials varied considerably. The anticoagulants tested were standard unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors. Over 90% of the evidence relates to the effects of anticoagulant therapy initiated within the first 48 hours of onset. Based on 11 trials (22,776 participants) there was no evidence that anticoagulant therapy started within the first 14 days of stroke onset reduced the odds of death from all causes (odds ratio (OR) 1.05; 95% confidence interval (CI) 0.98 to 1.12) at the end of follow-up. Similarly, based on eight trials (22,125 participants), there was no evidence that early anticoagulation reduced the odds of being dead or dependent at the end of follow-up (OR 0.99; 95% CI 0.93 to 1.04). Although early anticoagulant therapy was associated with fewer recurrent ischaemic strokes (OR 0.76; 95% CI 0.65 to 0.88), it was also associated with an increase in symptomatic intracranial haemorrhages (OR 2.55; 95% CI 1.95 to 3.33). Similarly, early anticoagulation

reduced the frequency of symptomatic pulmonary emboli (OR 0.60; 95% CI 0.44 to 0.81), but this benefit was offset by an increase in extracranial haemorrhages (OR 2.99; 95% CI 2.24 to 3.99).

Authors' conclusions

Since the last version of the review, no new relevant studies have been published and so there is no additional information to change the conclusions. Early anticoagulant therapy is not associated with net short- or long-term benefit in people with acute ischaemic stroke. Treatment with anticoagulants reduced recurrent stroke, deep vein thrombosis and pulmonary embolism, but increased bleeding risk. The data do not support the routine use of any of the currently available anticoagulants in acute ischaemic stroke.

PLAIN LANGUAGE SUMMARY

Anticoagulants for acute ischaemic stroke

Millions of people around the world have strokes every year. Most strokes take place when a blood clot blocks a blood vessel leading to the brain. Without a proper blood supply, the brain quickly suffers damage, which can be permanent. The damage from a stroke can cause arm or leg weakness, or difficulties with language or vision. Strokes are sometimes fatal, but will more often leave the survivor unable to do the things that they used to do. Because strokes are common and cause such damage, researchers are trying to find ways to get rid of the blood clot soon after the stroke happens. One way to do this is with blood thinning drugs called anticoagulants. If anticoagulants work, the bad effects of the stroke might be avoided. The main problem with anticoagulants is that they can cause bleeding, which can sometimes be very serious. This systematic review was designed to find out whether people treated with anticoagulants soon after having a stroke got better or not, and whether they had problems with bleeding. There is a lot of information in this systematic review - 23,748 people with stroke have been involved in 24 included randomised trials to answer this question. People treated with anticoagulants did not have less long-term disability, and experienced more bleeding. Anticoagulant treated patients had less chance of developing blood clots in their legs and in their lungs following their stroke, but these benefits were offset by the increased number of bleeds. This review did not provide any evidence that the early use of anticoagulants is of overall benefit to people with strokes caused by blood clots. More research is needed to find out if there are ways to select the people with stroke who will benefit from anticoagulants without suffering the bleeding complications.

BACKGROUND

Description of the condition

Ischaemic stroke is usually caused by a blood clot blocking flow in an artery supplying parts of the brain and, in Western countries, is approximately 10 times more frequent than haemorrhagic stroke (Andersen 2009). Stroke is the second most common cause of death in the world (Lozano 2012) and the third most common cause of disability (Murray 2012). Globally, death and disability that result from stroke have been increasing in absolute numbers, with the greatest burden being in low and middle income countries (Feigin 2014).

Description of the intervention

Anticoagulants are agents acting on the coagulation cascade to reduce fibrin polymerisation and thrombus formation and are distinct from thrombolytic and defibrinogenating agents. Agents included in this review include unfractionated heparin, low-molecular-weight heparins, heparinoids, oral vitamin K antagonists and specific thrombin inhibitors. The control was an inactive intervention, either placebo or no treatment, delivered along with the standard interventions of the respective healthcare systems.

Heparins are administered parenterally (intravenously or subcutaneously) and so have a sufficiently rapid onset to be used in the acute phase of ischaemic stroke whereas oral anticoagulants, such as vitamin K antagonists and direct thrombin inhibitors, have a slower onset of effect and may be of less use. Unfractionated heparin, a sulphated polysaccharide, acts by binding to antithrombin to inhibit factor Xa and deactivate thrombin. Important side-effects include thrombocytopenia and osteopenia. Low molecular weight heparins are depolymerised heparin fragments approximately one third the size of unfractionated heparin and act primarily to inhibit factor Xa. They have a longer half-life, greater bio-availability and more predictable anticoagulant effect than unfractionated heparin. Heparinoids are glycosaminoglycans whose components catalyse the effect of heparin co-factor 2 to inhibit thrombin. All heparins ultimately prevent fibrin formation and subsequent thrombosis.

How the intervention might work

Theoretically, early use of anticoagulants may, by reducing the propagation of a thrombus in an intracerebral artery, decrease the volume of infarcted cerebral tissue and so decrease the neurological deficit, risk of disability and death. Additionally, anticoagulants might inhibit the formation of new arterial and venous thromboses and so reduce the risk of early recurrent thromboembolic stroke, deep vein thrombosis and pulmonary embolism. However, these benefits could be offset by the possibility that anticoagulant therapy increases risk of intracranial and extracranial haemorrhage.

Why it is important to do this review

This is an update of a Cochrane review first published in 1995, and most recently updated in 2008, encompassing all of the randomised trials of anticoagulants versus control in people with acute presumed or confirmed ischaemic stroke. The aim is to establish the balance of risk and benefit of early anticoagulation for acute ischaemic stroke.

OBJECTIVES

To assess the effectiveness and safety of early anticoagulation (within the first 14 days of onset) in people with acute presumed or confirmed ischaemic stroke. Our hypotheses were that, compared with a policy of avoiding their use, early anticoagulation would be associated with:

1. a reduced risk of being dead or dependent in activities of daily living a few months after stroke onset;
2. a reduced risk of early recurrent ischaemic stroke;
3. an increased risk of symptomatic intracranial and extracranial haemorrhage; and
4. a reduced risk of deep vein thrombosis and pulmonary embolism.

METHODS

Criteria for considering studies for this review

Types of studies

We sought all unconfounded, truly randomised trials in which early treatment with anticoagulants was compared with control in people with acute presumed or confirmed ischaemic stroke. People with ischaemic stroke due to cerebral venous thrombosis were not specifically included in these trials, and so are not represented in this review. People with transient ischaemic attacks (TIAs) are also not included in this review. We did not include trials in which allocation to treatment or control group was not truly random or where allocation was not adequately concealed (e.g. allocation by alternation, date of birth, hospital number, day of the week, or open random number list), since foreknowledge of treatment allocation could lead to biased treatment allocation, and thereby overestimate the treatment effect by up to 30% (Odgaard-Jensen 2011). We included trials if it was unclear whether the method of randomisation provided adequate concealment of allocation.

Types of participants

This review was confined to the early treatment of acute ischaemic stroke, and therefore we excluded the following types of trial: those that randomised participants more than 14 days after stroke onset, those that included only people with TIAs, and those that only included people with intracerebral haemorrhage, confirmed by appropriate brain imaging before entry. We included trials in which the pathological type of stroke was not confirmed by scanning before entry, as the majority of such strokes are ischaemic, at least in the white population (Bamford 1990).

Types of interventions

Anticoagulants are broadly defined as agents that act on the coagulation cascade to exert an anticoagulant effect, excluding thrombolytic agents (such as alteplase) and defibrinogenating agents (such as ancrod). The use of thrombolytic agents in acute ischaemic stroke is the subject of a separate Cochrane review (Wardlaw 2014), as is the use of fibrinogen depleting agents (Hao 2012). We included the following anticoagulants in this review: subcutaneous and intravenous standard unfractionated heparin, low-molecular-weight heparins, subcutaneous and intravenous heparinoids, oral vitamin K antagonists, factor Xa inhibitors and specific thrombin inhibitors.

Types of outcome measures

For each trial, we identified the number of participants originally randomly allocated to each treatment and control group. In both groups, we sought outcome information regarding the number of participants who met the following outcomes.

Primary outcomes

1. Death or dependency (i.e. people who were either dead, or dependent on help from other people for their activities of daily living), at least one month after their stroke. This minimum interval was used to allow time for recovery from the initial stroke. Comparable definitions of dependency were used in all of the trials assessed in this review.

Secondary outcomes

1. Participants who died from any cause during the scheduled treatment period (generally shorter than the scheduled follow-up period).
2. Participants who died from any cause during the scheduled follow-up period (greater than one month after their stroke).
3. Participants with objective evidence of deep vein thrombosis detected by the systematic use of imaging techniques such as iodine 125 fibrinogen scanning (I-125 scan), ultrasound of the leg, plethysmography, or X-ray contrast venography in all participants during the scheduled treatment period and during scheduled follow up. These methods therefore detected clinically silent deep vein thrombosis as well as confirming or refuting the diagnosis in participants with clinical features suggestive of deep vein thrombosis. The outcome was therefore 'symptomatic or asymptomatic deep vein thrombosis.' Screening of participants by clinical observation alone was not considered adequate.
4. Participants with at least one confirmed symptomatic pulmonary embolus diagnosed during life, or at autopsy (symptomatic or not) within the scheduled treatment period and during scheduled follow-up.
5. Particpants with recurrent stroke during the treatment period and during follow-up, which was either definitely ischaemic (haemorrhage excluded by brain imaging or autopsy), or of unknown type (no brain imaging or autopsy performed).
6. Participants with symptomatic intracranial (intra or extracerebral) haemorrhage, including symptomatic haemorrhagic transformation of the cerebral infarct, during the scheduled treatment period and during follow-up. The haemorrhage must have been confirmed by appropriate brain imaging after clinical deterioration, or by autopsy.
7. Participants with any recurrent stroke or symptomatic intracranial haemorrhage during the treatment period or during long-term follow up (as previously defined).
8. Participants with any major extracranial haemorrhage during the scheduled treatment period. The definition of major haemorrhage was usually taken from the original article but if none was given it was defined as any fatal bleed, or bleeding severe enough to require transfusion or operation.

Although we sought trials that reported the primary outcome (dead or dependent at least one month after stroke), we also included data from trials that only reported data on our secondary outcomes.

Search methods for identification of studies

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

Electronic searches

We searched the Cochrane Stroke Group Trials Register (last searched June 2014) and the following bibliographic databases and trials registers:

- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014 Issue 6) (Appendix 1);
- Cochrane Database of Systematic Reviews (CDSR) (*The Cochrane Library* 2014 Issue 6) (Appendix 1);
- Database of Reviews of Effects (DARE) (*The Cochrane Library* 2014 Issue 6) (Appendix 1);
- Health Technology Assessment Database (HTA) (*The Cochrane Library* 2014 Issue 6) (Appendix 1);
- MEDLINE (Ovid; 2008 to June 2014) (Appendix 2);
- EMBASE (Ovid; 2008 to June 2014) (Appendix 3);
- ClinicalTrials.gov (https://clinicaltrials.gov; searched June 2014) (Appendix 4);
- Internet Stroke Center Stroke Trials Registry (http://www.strokecenter.org/trials/; searched June 2014) (Appendix 4);
- ISRCTN Registry (http://www.isrctn.com/; searched June 2014) (Appendix 4).

Using a comprehensive search strategy the Cochrane Stroke Group Trials Search Co-ordinator has already completed a retrospective search of MEDLINE and EMBASE for all stroke trials to January 2008 and added all relevant trials to the Cochrane Stroke Group Trials Register. To avoid duplication of effort we have limited the search of these two databases from January 2008 onwards.

Searching other resources

1. We scanned the reference lists of all relevant papers.
2. For previous versions of this review:
   a. we contacted the following anticoagulant manufacturers in an effort to identify unpublished trials (last contact 1999): Alfa Wasserman (parnaparin and dermatan sulphate), Kabi (dalteparin), Knoll (reviparin), Leo (tinzaparin), Mediolanum (dermatan sulphate), Mitsubishi Chemical (argatroban/MD-805), Novo (tinzaparin), Organon (danaparoid), Rhone-Poulenc Rorer (enoxaparin), Sandoz (Sandoz LMWH), Sanofi Winthrop (nadroparin and CY 222);
   b. we consulted a comprehensive guide to pharmaceutical development in the field of stroke (MedStrategy 1995) but have not updated the search, as relevant trials contained within it are in the Cochrane Stroke Group Trials Register;
   c. we searched the trials register held by the Antithrombotic Trialists' (ATT) Collaboration in August 1998, but this is no longer available and relevant trials from the register are now in the Cochrane Stroke Group Trials Register.

Data collection and analysis

For this update EK performed the searches following advice from Brenda Thomas (Cochrane Stroke Group Trials Search Co-ordinator). EK and PS then independently screened all the titles and abstracts of the identified references and excluded obviously irrelevant studies. EK obtained the full-text articles of the remaining studies and both EK and PS independently assessed these for inclusion or exclusion. We resolved any disagreements by discussion.

Selection of studies

Two review authors (PS & CC, for the trials included in the first version of this review; PS & Gordon Gubitz for the proceeding two updates following the original review, Ayeesha Kamal & PS for the most recent update and PS & EK for this review) independently selected trials for inclusion in the review. We resolved disagreements through discussion. The same two review authors assessed the methodological quality of each trial.

Data extraction and management

Two review authors independently extracted and cross-checked the data. We sought data on the number of participants with each outcome event, by allocated treatment group, irrespective of compliance, and whether or not the participant was subsequently deemed ineligible or otherwise excluded from treatment or follow-up, to allow an intention-to-treat (ITT) analysis. We also sought data on the use of brain imaging prior to randomisation, the delay from stroke onset to trial entry, the type of patients included, and the type of anticoagulant regimen used. If any of the above data were not available in the publications, we sought further information by correspondence with the trialists.

Assessment of risk of bias in included studies

For the previous versions of this review, two authors assessed the methodological quality of each trial. We did not use a scoring system to assess trial quality, but simply recorded details of randomisation and concealment methods, blinding, if ITT analyses were possible from the published data (that is, if there were any exclusions from the trial after randomisation) and if any participants were lost to follow-up. We sought data on the number of participants with each outcome event, by allocated treatment group, irrespective of compliance, and whether or not the participant was subsequently deemed ineligible or otherwise excluded from treatment or follow-up, to allow an ITT analysis.

Measures of treatment effect

The results reported in the text are odds ratios (OR: 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). We calculated the significance of any differences between ORs (in relation to subgroup analyses) using a standard method (Altman 1996). Where relevant, the absolute effects of treatment on each outcome are expressed as the number needed to treat to benefit (NNTB) i.e. to avoid one bad outcome event. For events that are adverse (such as intracranial haemorrhage), this is calculated as the number needed to treat to harm (NNTH). To calculate NNTBs or NNTHs, we used the NNT calculator at http://www.dcn.ed.ac.uk/csrg/entity/entity_NNT2.asp. This applies the point estimate of relative effect and its 95% confidence interval (CI), and then calculates the NNTB or NNTH for a specified control event rate.

Unit of analysis issues

All the included studies were trials in which individuals were randomised, and follow-up was generally to a prespecified and fixed time point, and all analyses were by ITT where possible (see Dealing with missing data). For outcomes where more than one event could occur during follow-up, such as non-fatal recurrent stroke, we counted only the first event.

Dealing with missing data

For some outcomes (such as deep vein thrombosis and any intracranial haemorrhage), ITT analyses were not possible because all participants did not have the relevant investigation performed to detect the event. In these analyses, we used the number of participants in each group who had the appropriate investigation as the denominator for the main analyses. However, if we found statistically significant results we also analysed best and worst case scenarios: the best-case scenario (with regards to treatment) assumed that none of the participants excluded from the analysis in the treatment group had an adverse outcome, whilst all those excluded from the control group did, and vice versa for the worst-case analysis.

Assessment of heterogeneity

We tested for heterogeneity between trial results with the I^2 test. We used the method described in Bland 2003 to test for interaction between the effect in a specified subgroup and the overall effect.

Assessment of reporting biases

We sought evidence of publication bias with funnel plots for three outcomes: deep vein thrombosis, death from all causes within the scheduled treatment period and death from all causes by the end of follow-up.

Data synthesis

We used RevMan 2014 for the analyses, in which we grouped together trials of each type of anticoagulant (e.g. unfractionated heparin, low-molecular-weight heparins, heparinoids, oral vitamin K antagonists, thrombin inhibitors) to assess whether there were any significant differences between classes of anticoagulant agent. It should be noted that this was an indirect rather than a direct randomised comparison.

We also specified the following classification of anticoagulant dosing regimens.

1. Low fixed-dose anticoagulant, that is a dose intended to be sufficient for the prevention of deep vein thrombosis and pulmonary embolism.
2. Medium fixed-dose anticoagulant, that is a dose intended to have effects on the arterial circulation, but not enough to require monitoring.
3. Adjusted-dose anticoagulant, that is a dose adjusted by blood testing or body weight to meet a specific target.

Subgroup analysis and investigation of heterogeneity

For this update, we performed subgroup analyses of:

- the type of anticoagulant agent used; and
- the dose of anticoagulant used, applying the classification above.

Sensitivity analysis

For this update, we performed the following sensitivity analyses, restricting analyses to:

- trials in which the method of randomisation ensured adequate concealment of treatment allocation;
- trials in which all participants were recruited within 48 hours of stroke onset; and
- trials except IST 1997, as this trial contained most of the data for the review.

In the previous version of this review we performed numerous sensitivity analyses to investigate whether the exclusion or inclusion of trials with particular characteristics would alter the overall conclusions. These characteristics included: trials that had intracerebral haemorrhages excluded by neuroimaging prior to trial entry, time from stroke onset (less than 48 hours versus more than 48 hours) to randomisation, concomitant unconfounded treatment with antiplatelet agents, trials in which stroke was of suspected cardioembolic origin versus non-cardioembolic origin, and trials that evaluated different anticoagulant doses. These analyses were not informative and we have excluded them from this updated review for brevity and clarity. In future updates of the review, we do not plan to repeat these analyses unless substantial new trial data had been added.

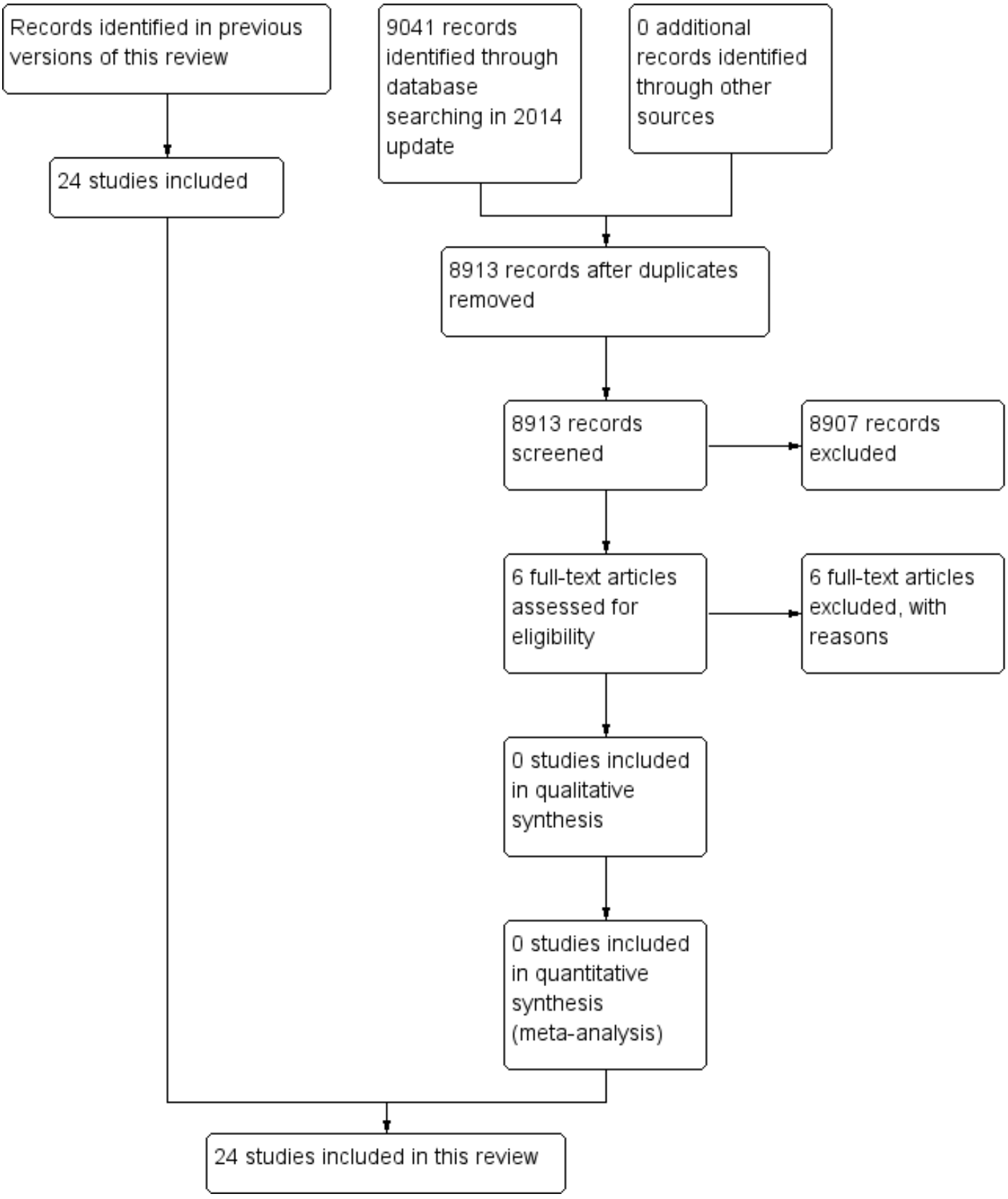
RESULTS

Description of studies

Results of the search

For this update we searched the Cochrane Stroke Group Trials Register and performed additional new comprehensive searches of The Cochrane Library databases, MEDLINE and EMBASE. After removal of duplicate records we screened the titles and abstracts of 8913 records from these electronic bibliographic databases and obtained the full text of six studies, all of which we excluded leaving no new trials for inclusion. The total number of included studies remains unchanged from the last update at 24 trials. See Figure 1.

Figure 1. Study flow diagram for 2014 update



We identified one new ongoing trial from searches of the trials registers (see Characteristics of ongoing studies).

Included studies

We included 24 trials with a total of 23,748 participants in this review. Summary details of the trials are given in the 'Characteristics of included studies' table. Of the 24 included studies, one enrolled participants within 12 hours of stroke onset (ARGIS-1 2004), two enrolled participants within 24 hours of stroke onset (FISS-bis 1998; TOAST 1998), 10 enrolled participants within 48 hours of stroke onset (Cazzato 1989; CESG 1983; Duke 1983; Duke 1986; Elias 1990; FISS 1995; IST 1997; Kwiecinski 1995; McCarthy 1977; McCarthy 1986), and the rest enrolled participants within 14 days. The age of participants in the included studies ranged from 28 to 92 years. A significant proportion of participants were over 70 years old. For example, 61% of participants enrolled in IST 1997 were aged 70 or older. Most trials included slightly more males than females. Most trials excluded people thought to be at high risk of bleeding (e.g. clotting disorders, hepatic or renal failure). In addition, 10 trials excluded people with significant degrees of hypertension (generally diastolic pressures greater than 120 mmHg or systolic pressures greater than 180 mmHg), and nine trials excluded comatose people.

The scheduled period of anticoagulant treatment in the included trials was one to two weeks in 20 trials and one month in four trials. The anticoagulants used were:

- standard unfractionated subcutaneous heparin (six trials);
- standard unfractionated intravenous heparin (two trials);
- low-molecular-weight heparins (eight trials: two dalteparin, two nadroparin, one tinzaparin, one fraxiparin, one parnaparin, and one CY 222);
- subcutaneous heparinoid (two trials: one danaparoid and one mesoglycan);
- intravenous heparinoid (one danaparoid trial);
- oral vitamin K antagonists (two trials); and
- thrombin inhibitors (three trials: two MD805 trials, one argatroban).

In the trials using oral vitamin K antagonists, heparin was given intravenously for the first few days to provide rapid anticoagulation (Marshall 1960; NAT-COOP 1962). Three trials randomised between two doses of anticoagulant as well as control (FISS 1995; FISS-bis 1998; IST 1997); for the main analyses in this review we combined the two anticoagulant groups for these trials.

Fifteen trials routinely performed a CT head scan in all patients to rule out haemorrhage before randomisation (ARGIS-1 2004; Cazzato 1989; CESG 1983; Duke 1986; Elias 1990; FISS 1995; FISS-bis 1998; Kwiecinski 1995; Pambianco 1995; Prins 1989; Sandset 1990; Tazaki 1986; Tazaki 1992; TOAST 1998; Turpie 1987). Three trials performed CT in most patients (Duke 1983; IST 1997; Vissinger 1995): eighty-one per cent of participants in Duke 1983 were scanned; in IST 1997, 67% were scanned before randomisation, and 29% after randomisation, so that overall, 96% of participants were scanned; in Vissinger 1995, 66% of participants were scanned, and the remainder had cerebral scintigraphy to exclude haemorrhage. Three trials performed almost no CT scans (McCarthy 1977; McCarthy 1986; Pince 1981), and two trials were undertaken before CT scanning was introduced (Marshall 1960; NAT-COOP 1962). It is therefore likely that some people with intracerebral haemorrhage were inadvertently included in the main analyses of this review. This may have biased the results against anticoagulation if the risks of anticoagulation are greater in those with intracerebral haemorrhage, although such a bias is unlikely given the relatively small numbers of people with intracerebral haemorrhage involved in these trials, and because IST 1997 provided well over 80% of the overall data.

Two trials included only participants with presumed cardioembolic stroke (CESG 1983; NAT-COOP 1962). One trial enrolled a subset of people with atrial fibrillation (IST 1997) and detailed information on the effect of heparin in this subgroup was reported in a paper published in 2001 (Saxena 2001).

The duration of follow-up in the trials was generally short, although this was mainly a characteristic of the smaller trials, which contributed less to the overall analysis. Four trials in which the primary outcome of interest was deep vein thrombosis did not follow the participants beyond 14 days (Elias 1990; McCarthy 1977; Pince 1981; Prins 1989), and only 11 trials followed participants for longer than one month (ARGIS-1 2004; Chaudhary 2002; Duke 1986; FISS 1995; FISS-bis 1998; IST 1997; Kwiecinski 1995; Marshall 1960; McCarthy 1986; TOAST 1998; Turpie 1987). This lack of long-term follow-up is a weakness of many of the smaller studies, as a significant proportion of deaths after one month could have been due to stroke-related thromboembolic events and might therefore have been prevented by early anticoagulation. Similarly, disability is best assessed when most of the recovery has taken place (that is between three to six months), rather than in the first week or so.

Relatively few trials assessed the clinically most important outcome of long-term functional status. Treatments that prevent death from stroke may lead to survival in a disabled state - an outcome considered by many to be worse than death. The composite outcome of 'dead or dependent at follow-up' is therefore the most important outcome in acute stroke trials. Eight trials assessed this composite outcome. These trials contain data from well over 90% of the participants included in this review, and evaluated the outcomes of death and dependency adequately (ARGIS-1 2004; Cazzato 1989; Chaudhary 2002; FISS 1995; FISS-bis 1998; IST 1997; Kwiecinski 1995; TOAST 1998). Other important outcomes, including recurrent stroke or intracranial haemorrhage, were assessed but, once again, only by the more recent trials that included large numbers of participants. Quality of life assessments were not undertaken in any of these trials.

Excluded studies

We excluded 31 studies for a variety of reasons (see Characteristics of excluded studies).

Risk of bias in included studies

Randomisation

There was marked variation in the quality of the trials. In 14 trials, the method of randomisation adequately prevented foreknowledge of treatment allocation. IST 1997 used a central telephone randomisation service. TOAST 1998 used permuted blocks to generate a randomisation list controlled by the hospital pharmacy. Eight trials utilised numbered or coded containers administered sequentially to enrolled participants (FISS 1995; FISS-bis 1998; Prins 1989; Sandset 1990; Tazaki 1986; Tazaki 1992; Turpie

1987; Vissinger 1995). Three trials used random-number tables controlled by an independent party (Cazzato 1989; Duke 1983; Duke 1986). The 2:1 treatment-to-control allocation ratio in Turpie 1987, Tazaki 1986, FISS 1995, and FISS-bis 1998 was deliberate. CESG 1983 used opaque sequentially-numbered envelopes. The method of randomisation was unclear in nine trials. Six trials stated that sealed envelopes were used but in five of these it was not clear whether or not the envelopes were opaque and sequentially numbered (Elias 1990; McCarthy 1977; McCarthy 1986; NAT-COOP 1962; Pince 1981). In Pambianco 1995 the envelopes were not numbered. The exact method of randomisation was unknown in ARGIS-1 2004, Chaudhary 2002, Kwiecinski 1995, and Marshall 1960.

Allocation

Allocation concealment for the following small trials was unclear: ARGIS-1 2004, Chaudhary 2002, Elias 1990, Kwiecinski 1995, Marshall 1960, McCarthy 1977, McCarthy 1986, Pambianco 1995, and Pince 1981. In the remainder we deemed allocation concealment adequate, with low risk of bias.

Blinding

Adequate blinding may be important to reduce bias in the detection of deep vein thrombosis, pulmonary embolism, symptomatic intracranial haemorrhage, recurrent stroke and functional outcome. Twelve trials were double-blind, that is treatment allocation was concealed from participants, physicians and outcome assessors (ARGIS-1 2004; Duke 1983; Duke 1986; FISS 1995; FISS-bis 1998; Prins 1989; Sandset 1990; Tazaki 1986; Tazaki 1992; TOAST 1998; Turpie 1987; Vissinger 1995), and in two other trials the assessment of deep vein thrombosis was made by radiologists blinded to treatment allocation (McCarthy 1977; McCarthy 1986). Cazzato 1989 had a blinded outcome assessor only. IST 1997 was not designed as a blinded study. However, an analysis of 207 participants from the UK enrolled in the IST pilot study showed that, at the six-month follow-up, the majority of participants could not remember whether or not they had been treated, and so these participants were effectively 'blinded' (Lindley 1993). In IST 1997, follow-up data were collected by self-completed questionnaire mailed to the participant six months after randomisation, or by telephone interview by a person blinded to treatment allocation. The remainder of the trials did not appear to use any form of blinded assessment.

Incomplete outcome data

In total, only 218 participants (0.9% overall) were reported to be excluded from analysis after randomisation or were lost to follow-up, with the vast majority of participants enrolled in studies in which an ITT analysis was performed. However, a number of participants in the smaller trials that did not report an ITT analysis may have been omitted from the analysis.

Selective reporting

We were only able to assess this for IST 1997 and did not have access to the original protocols of the remaining studies. There was no evidence of reporting bias for IST 1997.

Other potential sources of bias

Long-term use of antiplatelet agents

In trials with follow-up, differences in the long-term use of antiplatelet treatment between the anticoagulant and control groups after hospital discharge may have biased the results, as antiplatelet treatment has been shown to reduce the risk of further vascular events by about 25% (ATC 2002). Aspirin was given to all survivors in FISS 1995. Long-term treatment with aspirin was encouraged, but optional in several other trials, including IST 1997, FISS-bis 1998 and TOAST 1998. Aspirin (81 mg to 325 mg) was also used in both arms of the ARGIS-1 2004 trial of the direct thrombin inhibitor argatroban.

Imbalance at baseline

None of the trials reported significant imbalances in important baseline prognostic variables, although the small size of many suggests that they might only be ruling out substantial differences.

Effects of interventions

Outcome 1.1: Dead or dependent at end of follow up more than one month after randomisation

Eight trials including randomised data from 22,125 participants (93.2% of participants included in the overall review) evaluated death and long-term disability. The degree of dependence was determined by noting whether the participants required help from other people for their activities of daily living at the time of final follow-up. Treatment with early anticoagulation was not associated with a significant reduction in the odds of being dead or dependent at final follow up (odds ratio (OR) 0.99; 95% confidence interval (CI) 0.93 to 1.04, Analysis 1.1). There was, however, substantial heterogeneity of treatment effect (I^2 = 47.7%) between the different regimens included.

Subgroup analyses

By the type of anticoagulant agent used

The heterogeneity in the overall estimate was attributable to the non-significant trends to benefit associated with low-molecular-weight heparins and subcutaneous heparinoid regimens, and trend to harm associated with direct thrombin inhibitor (OR 1.28; 95% CI 0.62 to 2.62).

By the dose of anticoagulant agent

There was no statistically significant difference in death or dependence at final follow-up between trials in which low fixed-dose anticoagulants were compared with control (OR 1.00; 95% CI 0.92 to 1.08), or in which medium fixed-dose anticoagulants (OR 0.98; 95% CI 0.91 to 1.06) or adjusted-dose anticoagulants were compared with control (OR 0.95; 95% CI 0.75 to 1.20).

Sensitivity analyses

Sensitivity analyses restricted to:

- trials in which the method of randomisation ensured adequate concealment of treatment allocation showed that all of the trials evaluating death and dependence at final follow-up had adequate concealment of the randomisation process;
- trials that restricted entry to the study to less than 48 hours of stroke onset showed that all trials evaluating death or dependence at final follow-up enrolled participants within 48 hours of stroke onset. Within IST 1997 there was no evidence that the effect of treatment increased or decreased with increasing delay to randomisation up to 48 hours;

- trials other than IST 1997 (since it contained most of the data for the review) showed no apparent difference in the effect of treatment on death or dependence at final follow-up if data from IST were included (OR 0.99; 95% CI 0.94 to 1.05) or excluded (OR 0.92; 95% CI .78 to 1.09).

In a post-hoc sensitivity analysis to assess the impact of duration of follow-up on the estimate of effect for the primary outcome, exclusion of the trial with assessment of the primary outcome after only one month (Cazzato 1989) had no impact on the overall estimate of effect (OR 0.99; 95% CI 0.94, 1.04) or the degree of heterogeneity (I^2 = 55%).

Outcome 1.2: Death from all causes during the scheduled treatment period

Data from 21 trials, which included randomised data from 22,562 participants (95% of participants included in the review) were available for this outcome. Anticoagulants were not associated with a significant reduction in death at the end of the treatment period (OR 0.99; 95% CI 0.90 to 1.09, Analysis 1.2). There was no significant heterogeneity (I^2 = 15.8%).

Outcome 1.3: Death from all causes at final follow-up more than one month after randomisation

Data were available for 11 trials, which included 22,776 participants (95.9 % of participants included in the overall review). Anticoagulants were not associated with any significant reduction in the odds of death at final follow-up of greater than one month (OR 1.05; 95% CI 0.98 to 1.12, I^2 = 28.5%, Analysis 1.3).

Outcome 1.4: Deep vein thrombosis during the treatment period

Ten trials, which included randomised data from 916 participants (only 3.9% of participants included in the overall review), sought to systematically determine the effect of anticoagulants on the occurrence of 'symptomatic or asymptomatic deep vein thrombosis' at the end of the treatment period, as detected by:

- I-125 fibrinogen scanning (Duke 1983; Elias 1990; McCarthy 1977; McCarthy 1986; Pince 1981; Prins 1989; Turpie 1987);
- B-mode and Doppler ultrasound (Pambianco 1995); or
- X-ray contrast venography (Sandset 1990; Vissinger 1995).

Despite the small numbers of participants studied, anticoagulation was associated with a highly significant reduction in the odds of deep vein thrombosis (OR 0.21; 95% CI 0.15 to 0.29, Analysis 1.4), although the majority of deep vein thromboses detected were subclinical and asymptomatic. Assuming a control event rate of 15%, this would be equivalent to an NNTB of 9 (95% CI 9 to 10). To calculate NNTBs for different control event rates, we used the NNT calculator at http://www.dcn.ed.ac.uk/csrg/entity/entity_NNT2.asp. Fifteen participants (10 in the treatment group, five in the control group) did not have an adequate assessment of deep vein thrombosis and therefore we excluded them from this analysis, however even if we included these participants under a worst-case scenario the results did not change significantly (OR 0.23).

There was significant heterogeneity between the trial results (I^2 = 71.5%), which appeared to be due to three trials that did not show any clear effect of anticoagulation on the odds of deep vein thrombosis (Pambianco 1995; Sandset 1990; Vissinger 1995) and two trials that did (Elias 1990; McCarthy 1986). The three negative trials were the only ones that did not use I-125 fibrinogen scanning. One used ultrasound assessment (Pambianco 1995) while the other two used venography (Sandset 1990; Vissinger 1995). In addition, in one of these trials, participants were randomised up to 14 days after their initial stroke (Pambianco 1995) whereas the other trials all randomised participants within seven days. The two most positive trials had very small numbers of participants, with the resultant possibility that the results may have been due to chance. In addition, McCarthy 1986 (the most positive trial) was poorly concealed, introducing another potential source of bias.

Sensitivity analyses showed that there was no significant difference in the reduction in deep vein thrombosis from the above result if the analysis was restricted to trials where the concealment of allocation was secure (OR 0.45; 95% CI 0.26 to 0.78) or to trials in which radiographic assessment was blinded (OR 0.21; 95% CI 0.15 to 0.29). One of the trials excluded from this review did provide data on the numbers of deep vein thromboses in the participants by allocated treatment group (1/19 heparin, 3/27 placebo), but inclusion of these results did not significantly alter the analysis (Dahan 1986). No trials systematically sought to assess deep vein thrombosis after the end of the treatment period.

Outcome 1.5: Symptomatic pulmonary embolism during the treatment period

Fourteen trials, which included data from 22,544 participants (95.7% of participants included in the overall review), assessed reported fatal and non-fatal symptomatic pulmonary embolism, but no trial had systematically sought asymptomatic pulmonary embolism by performing ventilation-perfusion scans in all participants at the end of the treatment period. Anticoagulation was associated with a significant reduction in the odds of pulmonary embolism (OR 0.60; 95% CI 0.44 to 0.81, I^2 = 13.7%, Analysis 1.5).

In the trials described, the frequency of pulmonary embolism during the treatment period was variable, but quite low (1% in IST 1997 versus 7% in Elias 1990 and Prins 1989). Although not reported systematically, and thereby potentially under-reported, the rate of pulmonary embolism in IST 1997 in participants not receiving heparin was only 0.8%. This observation is supported by data from prospective hospital-based studies that have reported symptomatic pulmonary embolism as a complication in between 1% and 3% of patients with acute stroke (Davenport 1996). Applying the observed odds reduction in pulmonary embolism and assuming a control event rate of 2%, this effect translated into an NNTB of 127 (95% CI 91 to 268), although this may be an underestimate of the reduction in risk due to incomplete ascertainment.

Patients may continue to be at risk of pulmonary embolism after the early treatment period. This was suggested by data from three trials that continued to seek events systematically during the follow-up period (FISS 1995; TOAST 1998; Turpie 1987). Eight further pulmonary emboli were recorded, six of which were in the control group. The potential use of antiplatelet or anticoagulant agents after the trial period may have influenced the results of several trials (FISS 1995; TOAST 1998; Turpie 1987). One trial, with an 80% autopsy rate, did show a significant reduction in the risk of symptomatic and asymptomatic pulmonary embolism detected at

autopsy in the anticoagulation group (7/24 versus 33/47, OR 0.19; 95% CI 0.07 to 0.52) (McCarthy 1986).

Outcome 1.6: Recurrent ischaemic stroke or recurrent stroke of unknown pathological type during the treatment period

Eleven trials, which included 21,605 participants (90.9% of participants included in the overall review) systematically sought to record early recurrent strokes that were definitely ischaemic (CT scan excluded haemorrhage) or probably ischaemic, that is in which the cerebral pathology was unknown because a CT scan had not been performed. Anticoagulation was associated with a statistically significant reduction in recurrent ischaemic stroke (OR 0.76; 95% CI 0.65 to 0.88, I^2 = 0, Analysis 1.6) which, assuming a control event rate of 4%, translated into an NNTB of 108 (95% CI 74 to 266). The majority of the data (95%) were obtained from one trial (IST 1997).

Outcome 1.7: Symptomatic intracranial haemorrhage during the treatment period

Sixteen trials, which included randomised data from 22,943 participants (96.6% of participants included in the overall review) reported data on symptomatic (fatal and non-fatal) intracranial haemorrhage confirmed by CT scanning or autopsy. Early anticoagulation significantly increased symptomatic intracranial haemorrhages by more than twofold (OR 2.55; 95% CI 1.95 to 3.33, I^2 = 0, Analysis 1.7). Assuming a control event rate of 0.5%, this is equivalent to a NNTH of 131 (95% CI 88 to 213). The majority of data (76%) were contributed by one trial (IST 1997).

There was no significant heterogeneity in the excess of haemorrhages with different types of heparin. However, within IST 1997, intracranial haemorrhage significantly increased with increasing heparin dose. Participants allocated to avoid heparin, low-dose heparin, and medium-dose heparin had rates of intracranial haemorrhage of 0.3%, 0.7% and 1.8% respectively.

There is the possibility of some bias within these data, as there may have been a lower threshold for rescanning participants who had deteriorated clinically if they were known to be receiving anticoagulants (for example in IST 1997, which was not blinded). In addition, even in blinded trials, a physician is likely to be unblinded if bruising is observed at heparin injection sites. An unbiased assessment of the effect of anticoagulants on the occurrence of intracranial haemorrhage would come from systematic studies, in which all participants undergo a CT scan before the beginning of treatment to exclude haemorrhage, and all survivors have a repeat CT scan at the end of the scheduled treatment period, regardless of their clinical status. In such an unbiased assessment, all participants who died during the study would also have to undergo an autopsy. Unfortunately, it is rarely possible to achieve repeat CT scans in all survivors, or autopsies in all deaths. Five trials in this review made a systematic attempt to detect both symptomatic and asymptomatic intracranial haemorrhage in this way (ARGIS-1 2004; CESG 1983; FISS 1995; Prins 1989; Sandset 1990). All of the confirmed intracranial haemorrhages were intracerebral. In FISS 1995 the use of systematic CT scanning was introduced during the trial and so not all participants were eligible for this analysis. However, the numbers of participants and events in this analysis were small (symptomatic plus asymptomatic haemorrhages occurring in 20/266 participants (7.5%) allocated anticoagulant versus 27/264 control participants (10.2%)) so the estimate of risk of 'symptomatic plus asymptomatic' haemorrhage is imprecise (OR 0.76; 95% CI 0.38 to 1.52). In these trials, 25 participants (5% overall, 15 treated versus 10 control) did not have a repeat CT scan or autopsy. Including these 25 participants in hypothetical best and worst-case analyses changed the odds ratio significantly (OR 0.44 and 1.44 respectively), which suggests that the results are compatible with either substantial reductions or increases in the risk of 'symptomatic plus asymptomatic' intracranial haemorrhages with treatment.

Outcome 1.8: Any recurrent stroke or symptomatic intracranial haemorrhage during the treatment period and during long-term follow-up

Early anticoagulation reduces the odds of ischaemic stroke but also increases the odds of symptomatic intracranial haemorrhage. An outcome that combines these two (without double counting - that is, each participant is counted only once, even if both events occurred, with the first event being the one which is included) is useful for assessing the net short-term effects of anticoagulants. Eleven trials, which included randomised data from 21,605 participants (96.0% of participants included in the overall review), evaluated the occurrence of 'any recurrent stroke or symptomatic intracranial haemorrhage' during the treatment period. Anticoagulation was not associated with a net reduction in the odds of this outcome (OR 0.97; 95% CI 0.85 to 1.11, I^2 = 31.3%, Analysis 1.8). The majority of the data (93.6%) were obtained from IST 1997. An analysis of the recurrent strokes or intracranial haemorrhages during the follow-up period could only include data from three small studies (FISS 1995; Marshall 1960; Turpie 1987). There were far too few events for a reliable analysis.

Outcome 1.9: Major extracranial haemorrhage during the treatment period

Eighteen trials, which included randomised data from 22,255 participants (93.7 % of participants included in the overall review), reported data on major extracranial haemorrhage (defined as bleeding serious enough to cause death or require hospitalisation or transfusion). Anticoagulation was associated with a significant three-fold increase in major extracranial haemorrhage (OR 2.99; 95% CI 2.24 to 3.99, I^2 = 4%, Analysis 1.9). Assuming a control event rate of 0.4%, this is equivalent to an NNTH of 128 (95% CI 85 to 204).

Publication bias

To determine whether or not we might have missed an important number of small negative trials (these are the trials most likely to remain unpublished) we undertook a funnel plot analysis (Egger 1997). The analyses with the most number of trials included (and hence the greatest statistical power) were the effects of treatment on death during the treatment period (Figure 2), death from all causes at final follow-up (Figure 3) and deep vein thrombosis (Figure 4). For these outcomes, a plot of the sample size for each trial versus the odds ratio for that trial showed an approximate 'funnel distribution' with 'tails' in both the positive and negative treatment effect directions (except in the outcome of deep vein thrombosis) indicating that we were unlikely to have missed a substantial number of negative trials.

Figure 2. Death from all causes during the treatment period

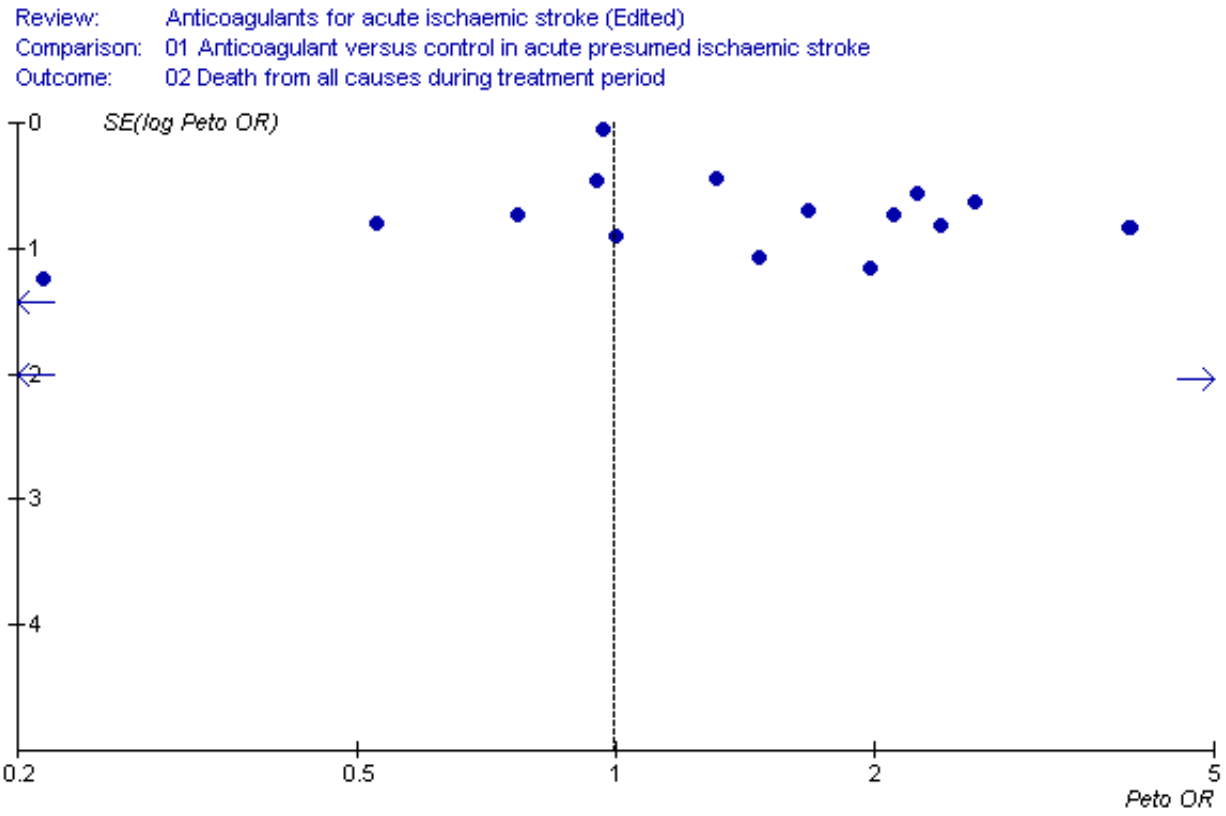


Figure 3. Death from all causes during final follow up

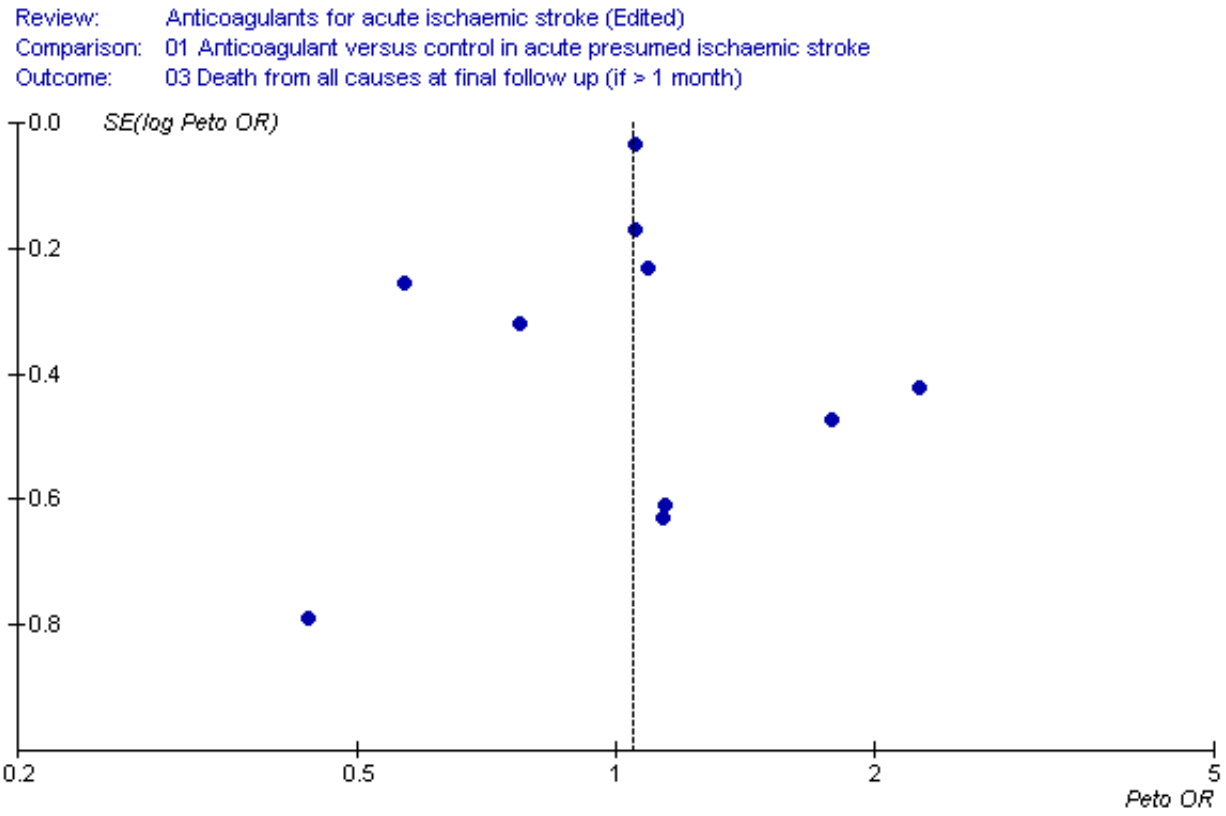
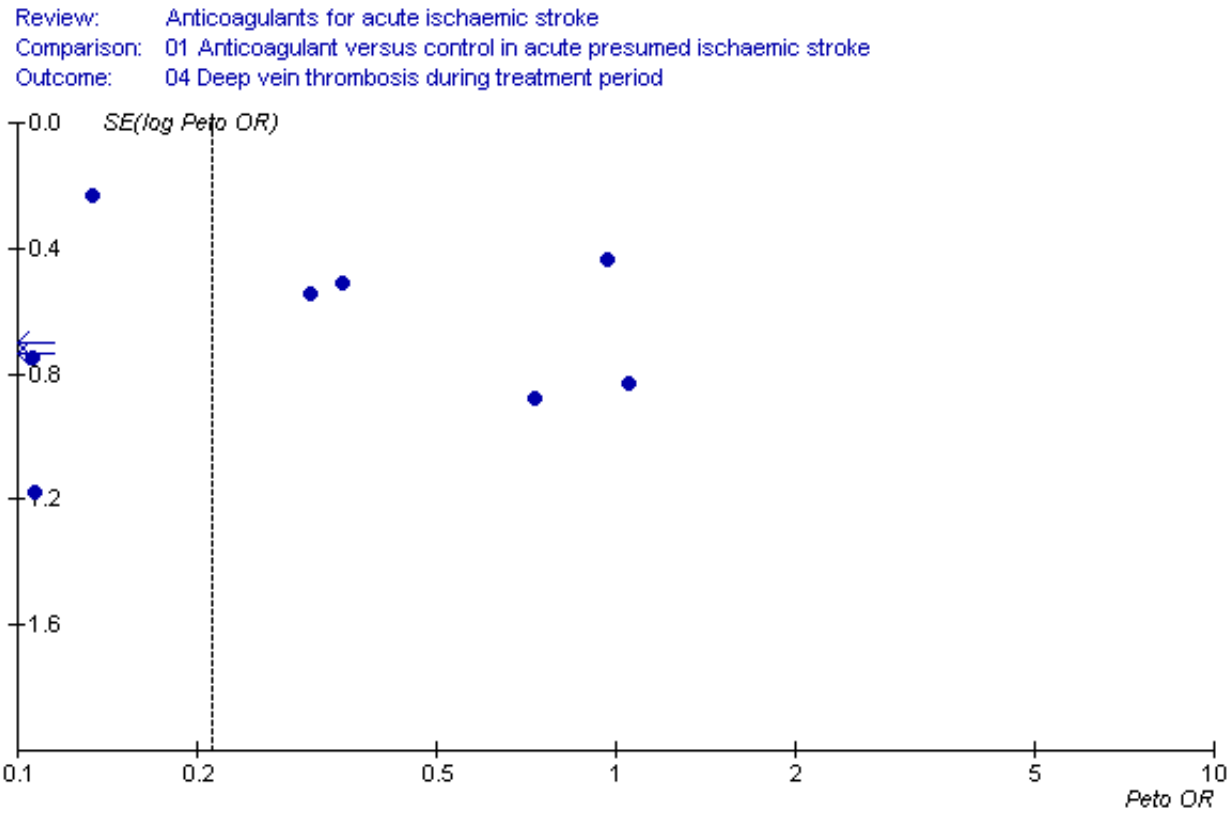


Figure 4. Funnel plot of deep vein thrombosis during follow-up showing asymmetry



DISCUSSION

The evidence provided in this updated systematic review has not changed any of the conclusions of the previous review published in 2008, and can be summarised as follows.

Summary of main results

Net effect of early anticoagulants in acute ischaemic stroke

Acute stroke treatments should aim to prevent disability as well as death, lest patients survive their acute stroke only to remain severely disabled. The currently available evidence from randomised trials indicates that routine early anticoagulation does not provide any significant net short or long-term reduction in death or disability. Although early anticoagulation leads to fewer recurrent ischaemic strokes (NNTB 108), this benefit is entirely offset by a similar-sized increase in intracranial haemorrhages (NNTH 131). The net result is no short or long-term benefit.

Hazards of early anticoagulants in acute ischaemic stroke

In order to be useful, a medical therapy must be safe. The current evidence from randomised trials demonstrates a clinically and statistically significant risk of major intra and extracranial haemorrhage with the early use of anticoagulants in people with acute ischaemic stroke.

Different anticoagulant agents, doses and routes of administration

The present evidence from randomised trials does not suggest that any one anticoagulant regimen is superior to any other. Indirect comparisons of unfractionated heparin, low-molecular-weight heparin, heparinoids and specific thrombin inhibitors have shown no significant net benefit in terms of reducing death during the treatment period, or death or dependency after follow-up greater than one month. Direct comparisons of different anticoagulants show no clear benefit of heparinoids versus unfractionated heparin (Sandercock 2008). The available evidence does not support the routine use of adjusted-dose intravenous heparin (or heparinoid) regimens, or of more intensive fixed-dose regimens.

Prevention of deep vein thrombosis and pulmonary embolism in acute ischaemic stroke with anticoagulants

In participants with presumed or confirmed ischaemic stroke, allocation to early anticoagulation was associated with a highly significant 79% reduction in the odds of deep vein thrombosis during the treatment period, similar to that seen with the use of prophylactic heparin in people undergoing different types of surgery (Collins 1988). In this review, the reductions in deep vein thrombosis with acute anticoagulation were statistically significant, though this estimate is based on relatively small numbers of participants, and most of the deep vein thromboses detected were asymptomatic. There was also significant heterogeneity in the effects of treatment, which renders the overall estimate less reliable.

The clinical significance of this reduction depends critically on the control event rate. In the included studies, there was substantial variation in the control event rate from 13% in Vissinger 1995 to 73% in McCarthy 1986. The rate will depend on many factors such as the severity of the stroke, the presence of leg paralysis and a history of previous deep vein thrombosis (Warlow 2008). The odds of pulmonary embolism were reduced significantly with the use of anticoagulants by 40%. In the included trials, pulmonary embolism was uncommon, so assuming the 0.8% control rate seen in the largest trial with the most representative sample of participants (IST 1997), the NNTB was 315, though with a perhaps more realistic control event rate of 2% it would be 127. The overall risk of pulmonary embolism appeared to be low, and the absolute benefit was small, and so the apparent reduction in deep vein thrombosis may have little clinical relevance if there is not a correspondingly large reduction in pulmonary embolism. However, there may well have been under-ascertainment of pulmonary embolism in all of the trials, since data on pulmonary emboli were not sought systematically. In addition, deep vein thrombosis can lead to morbidity (such as post-phlebitic leg and varicose ulcers), but data on these outcomes were not available from the trials. Finally, it is possible that once anticoagulants are stopped, rebound thrombosis could occur, and deep vein thromboses may begin to develop. We were unable to exclude this possibility because no trials sought data on deep vein thrombosis systematically after the treatment period.

If anticoagulants result in no net increase or decrease in long-term death or disability, but do lead to a reduction in the number of deep vein thromboses and pulmonary emboli (albeit in immobile patients at higher risk), then the benefit of fixed heparin regimens associated with a low risk of bleeding (for example low fixed-dose unfractionated or low-molecular weight heparin) may yet outweigh the increased risk of haemorrhage. A low deep vein thrombosis risk reduces the justification for unselective thromboprophylaxis with heparin. In IST 1997 the frequency of fatal and non-fatal symptomatic pulmonary embolism (perhaps a surrogate for the occurrence of deep vein thrombosis) was very similar among participants allocated low-dose subcutaneous heparin alone (0.8%) and aspirin alone (0.7%). Aspirin alone may therefore be an adequate antithrombotic agent to be used for routine deep vein thrombosis prophylaxis in some people with acute ischaemic stroke, as antiplatelet drugs, when used for prophylaxis of deep vein thrombosis and pulmonary embolism prophylaxis in other categories of high-risk patients are of modest benefit (ATC 2002). The recent CLOTS-3 2013 study has demonstrated that for people with ischaemic and haemorrhagic stroke, intermittent pneumatic compression reduces the risk of deep vein thrombosis after stroke, without any increased bleeding risk, and is effective both in the presence and absence of background heparin therapy.

The effects observed on deep vein thrombosis and pulmonary embolism in the present review indicate there might be a net benefit of low-dose heparin regimens among patients who are at high risk of venous thromboembolism, but at relatively low risk of intracranial or major extracranial bleeding. PREVAIL 2007 illustrates some of the difficulty in identifying subgroups who might have a favourable balance of risk and benefit. In that study, although the risk of venous thromboembolism (VTE) (symptomatic plus asymptomatic) was significantly lower among participants allocated enoxaparin, the study could not exclude a 69% increase in the risk of death up to day 14 and a 134% increase in the risk of intracranial haemorrhage with enoxaparin. This was because the event rates for the more major clinical outcomes were low: among the participants allocated unfractionated heparin, pulmonary embolism occurred in 1% and intracerebral haemorrhage in 1%. With such low event rates, conducting randomised trials large enough to reliably determine the balance of risk and benefit on these major clinical outcomes is challenging. In conclusion, the data from the present review were insufficient to reliably identify a subgroup that might benefit from heparin for thromboprophylaxis.

Overall completeness and applicability of evidence

This systematic review provides information about the use of anticoagulants in unselected people with ischaemic stroke as well as limited information about various subgroups. Given that many of the trials were conducted more than 20 years ago, are these results still relevant to clinical practice in the 21st century? In the sense that they represent the totality of evidence comparing treatment with control, they remain relevant to current practice in many parts of the world and continue to be cited in stroke treatment guidelines. The pattern of background treatment has changed, with many patients now being treated within organised stroke units (in the developed world at least). This might have an impact on the absolute risks and benefit of anticoagulation, but is less likely to influence the estimates of relative effect, and hence - in our view - the results remain relevant. Anticoagulants are also sometimes advocated for the treatment of acute carotid dissection and cerebral venous thrombosis. Separate Cochrane reviews have been prepared for these topics (Lyrer 2010; Coutinho 2011). We were reluctant to pursue further subgroup analysis, since it is hazardous to explore subgroup effects when there is no significant overall effect of an intervention on major outcomes and we only had access to major outcomes. A more detailed assessment of the effects of anticoagulants in other categories of patient (for example patients treated within three hours, patients with large-artery strokes, patients with carotid stenosis) would however, be possible with an individual patient data meta-analysis.

The stroke patients included in the trials of anticoagulants to prevent deep vein thrombosis generally had quite severe strokes, and paralysis of one leg (with the attendant high risk of deep vein thrombosis) was almost invariably present at randomisation. If, however, one accepts the estimate of treatment effect from these trials in the 1980s and 1990s, it is then difficult to assess the extent to which it may be generalisable to clinical practice from 2000 onwards. In current practice, the risk of deep vein thrombosis may well be low, since many patients are admitted to stroke units, receive aspirin, maintain good hydration, and are generally mobilised early.

With that qualification in mind, the small amounts of (randomised) subgroup data evaluated here do not provide any evidence to support the routine use of anticoagulants in any specific category of stroke patient.

Quality of the evidence

The bulk of the evidence in this review comes from trials with adequate allocation concealment, which is a strength. However, IST 1997 - by far the largest trial - was unblinded - which may well have led to ascertainment bias especially for the early outcomes. The final outcome, however, was assessed at a time when patients could not accurately recall their treatment allocation, so in all

likelihood the assessment of the primary outcome was probably not materially biased.

Potential biases in the review process

This review is based on an analysis of tabular data, which limits the extent to which effects in subgroups can be explored. However, an individual patient data meta-analysis has been performed. The included trials measured the primary outcome at differing times after randomisation, ranging from one to six months after randomisation, as we did not have access to individual patient level data to calculate person-days or hazard ratios. In considering the impact of differing lengths of follow-up on the primary outcome, a post hoc-sensitivity analysis excluding the study with less than three months follow-up did not alter the overall estimate of effect or reduce the heterogeneity.

Agreements and disagreements with other studies or reviews

Lederle 2011 is a systematic review of venous thromboembolism prophylaxis in hospitalised medical patients and those with stroke, and concluded "Heparin prophylaxis had no significant effect on mortality, may have reduced PE (pulmonary embolism) in medical patients and all patients combined, and led to more bleeding and major bleeding events, thus resulting in little or no net benefit. No differences in benefits or harms were found according to type of heparin used." Similarly, there was no clear difference in effects between people with stroke and with other non-surgical causes for hospital admission. A number of guideline statements have since been developed; the most recent American Stroke Association Guidelines (AHA Guidelines 2012) include two specific recommendations that are supported by the evidence provided in this systematic review. These are as follows.

- Urgent anticoagulation, with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after acute ischaemic stroke, is not recommended for treatment of patients with acute ischaemic stroke.
- At present, the usefulness of argatroban or other thrombin inhibitors for treatment of patients with acute ischaemic stroke is not well established.

An individual patient data meta-analysis of the large trials of heparin in acute ischaemic stroke was recently able to explore subgroup effects in greater detail, with the aim of identifying the subgroup of patients most likely to derive net benefit from heparin. However, the authors concluded: "There was no evidence that patients with ischaemic stroke who were at higher risk of thrombotic events or lower risk of haemorrhagic events benefited from heparins. We were, therefore, unable to define a targeted approach to select the patients who would benefit from treatment with early anticoagulant therapy." (Whiteley 2013).

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from this systematic review indicates that, compared with control, the types of anticoagulants tested in people with acute ischaemic stroke have no effect in terms of death in the short term, or death or dependency after follow-up of at least one month. A reduction in recurrent ischaemic stroke during the treatment period is exactly offset by an increase in intracranial haemorrhage. Although anticoagulants decrease deep vein thrombosis and pulmonary embolus, these benefits are once again offset by similar-sized increases in extracranial haemorrhage.

The data do not support the routine use of early high-dose intravenous or subcutaneous anticoagulants in any form for people with acute ischaemic stroke. Low-dose subcutaneous regimens will prevent deep vein thrombosis, but with a small but definite increased risk of major haemorrhage. It may therefore be advisable to consider safer alternatives in immobile patients (such as aspirin, compression stockings, or early mobilisation).

The data reviewed from trials comparing these agents with control do not support the use of low-molecular-weight heparins, heparinoids or thrombin inhibitors in the treatment of acute ischaemic stroke.

The analysis performed did not identify any category of patient where there was clear net benefit. Clinicians who feel compelled to use early anticoagulants for specific categories of patients following acute ischaemic stroke should weigh any potential theoretical benefits with the known risk of bleeding. Aspirin is an effective antithrombotic alternative to anticoagulation that is safe when used in the acute phase of ischaemic stroke.

Implications for research

This review has not provided reliable evidence on a number of important categories of patient with acute cerebrovascular disease who might plausibly derive net benefit from early anticoagulation (very recent transient ischaemic attacks (within hours or days of onset), crescendo transient ischaemic attacks and progressing ischaemic stroke are a few examples) and further trials targeted at these groups (perhaps with new agents) may be warranted. The choice of comparator agent against which to test any anticoagulant will depend on a number of factors, but further trials comparing anticoagulants against control seem unlikely.

Those clinicians who wish to continue to use intensive intravenous dose-adjusted heparin regimens routinely to treat specific categories of stroke patient should provide convincing evidence from new randomised controlled trials to support such practices.

This review has not provided clear evidence about the optimum antithrombotic regimen for the prevention of deep vein thrombosis and pulmonary embolism in stroke patients. Aspirin alone, low-dose subcutaneous heparin, and the use of graded compression stockings are all promising possibilities, but a very large scale randomised trial with several tens of thousands of participants would be required to determine which (or which combination) has the most favourable balance of risk and benefit on overall clinical outcome.

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of the early trials; Dr E Dick for supplying us with a copy of the MedStrategy document 'Stroke: A focus on opportunity'; Dr AGM van den Belt and Dr RI Lindley who helped produce the previously published version of this review (Sandercock 1993); and Hazel Fraser for supplying regular lists of trials identified by the Cochrane Stroke Group's search strategy. David Signorini was a co-author of an earlier version of the review. Dr Gord Gubitz contributed to earlier versions of this review. We also acknowledge the help given by the secretariat of the Antithrombotic Trialists' Collaboration (Dr C Baigent, Dr C Sudlow). We would like to acknowledge Brenda Thomas, Steff Lewis and Hazel Fraser of the Cochrane Stroke Group for their input and expertise in completing the update of this review.

Ongoing trials

Anyone who knows of additional trials that we have omitted, please write to Dr Peter Sandercock.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

ARGIS-1 2004

Methods	C = randomisation not described Patient, doctor and assessments blinded Exclusions during the trial: none

ARGIS-1 2004 *(Continued)*

	Losses to FU: 5 participants
Participants	North America 171 participants Mean age 65 years 100% CT before entry Mild to moderate ischaemic stroke NIHSS 7 to 22 Less than 12 hours since onset
Interventions	Rx: argatroban 100 mcg/kg bolus, followed by low-dose arm 1 mcg/kg/min or high-dose arm 3 mcg/kg/min for 5 days versus placebo Control: aspirin use in both arms
Outcomes	Death Symptomatic ICH Major extracranial ICH Barthel, NIHSS, MRS at 90 days
Notes	Ex: age > 85 BP: > 220/130 FU: 30 days, 90 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Cazzato 1989

Methods	C = random number table controlled by doctor not involved in treatment Outcome assessor blind Exclusions during trial: none Losses to FU: none
Participants	Italy 57 participants Mean age 68 years 49% male 100% CT before entry Ischaemic stroke Less than 48 hours since stroke onset
Interventions	Rx: mesoglycan (heparinoid) 50 mg 8 hourly im for 5 days, then 144 mg/day orally for 25 days Control: no treatment All participants received dexamethasone iv Duration: 30 days
Outcomes	Death plus cause of death Functional outcome (OHS 3, 4, 5 = dependent) PE (symptomatic plus autopsy in 9/10 deaths) Intracranial haemorrhage (symptomatic CT) Recurrent stroke Major extracranial haemorrhage
Notes	Ex: none

Cazzato 1989 *(Continued)*

	FU: 30 days

Risk of bias

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

CESG 1983

Methods	C = sealed envelopes (opaque and sequentially numbered) Non-blind Exclusions during trial: none Losses to FU: none
Participants	North America 45 participants 42 to 83 years 58% male 100% CT before entry Cardioembolic stroke Less than 48 hours since stroke onset
Interventions	Rx: heparin iv (continuous, APTT 1.5 to 2.5) +/- coumadin Control: no treatment Duration: 10 days
Outcomes	Death plus cause of death Intracranial haemorrhage (systematic CT on day 4 to 10) Recurrent stroke Major extracranial haemorrhage
Notes	Ex: BP > 180/115, bleeding risk FU: 14 days

Risk of bias

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

Chaudhary 2002

Methods	C = randomisation not described Assessment not blinded Exclusions during trial: none Losses to FU: none
Participants	India 30 participants 65 years 100% CT before entry

Chaudhary 2002 *(Continued)*

	Acute stroke - time not otherwise defined
Interventions	Rx: parnaparin 0.3 ml sc bid for 10 days versus placebo
Outcomes	Death and Barthel Index at 3 months
Notes	Ex: CT with ICH, coagulopathy

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Duke 1983

Methods	C = random number list controlled by pharmacy Doctor, patient, and assessor blind Exclusions during trial: none Losses to FU: none
Participants	Canada 65 participants ? age ? sex 81% CT before entry 'Partial stable' ischaemic stroke < 48 hours since stroke onset
Interventions	Rx: heparin 5000 IU sc 8 hourly Control: placebo Duration: 7 days
Outcomes	Death DVT (systematic I-125 scan) Intracranial haemorrhage (symptomatic) Extracranial haemorrhage
Notes	Ex: BP > 120 diastolic, bleeding risk FU: 1 year

Risk of bias

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

Duke 1986

Methods	C = random number list controlled by pharmacy Doctor, patient, and assessor blind Exclusions during trial: none

Duke 1986 *(Continued)*

	Losses to FU: 3 participants (number in each group unknown)
Participants	Canada 225 participants Mean age 67 years 63% male 100% CT before entry 'Partial stable' non-cardioembolic ischaemic stroke < 48hrs since stroke onset
Interventions	Rx: heparin iv (continuous, APTT 50 to 70 seconds) Control: placebo Duration: 7 days Antiplatelet therapy during follow up not reported
Outcomes	Death but not cause of death Functional outcome (measured but not reported) Intracranial haemorrhage (symptomatic)
Notes	Ex: BP > 110 diastolic, coma FU: 1 year

Risk of bias

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

Elias 1990

Methods	C = sealed envelopes (? opaque and sequentially numbered) Non-blind Exclusions during trial: none Losses to FU: 2 in Rx group
Participants	Europe 30 participants Mean age 68 years 57% male 100% CT before entry Ischaemic stroke with immobility Less than 48 hours since stroke onset
Interventions	Rx: CY 222 (LMWH) 15,000 anti-Xa units sc 24 hourly Control: no treatment Duration: 14 days
Outcomes	Death plus cause of death DVT (systematic I-125 scan, venography 50%) Major extracranial haemorrhage
Notes	Ex: BP > 220/120, coma FU: 14 days

Risk of bias

Elias 1990 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

FISS 1995

Methods	C = sequentially numbered boxes containing identical syringes Doctor, patient, and assessor blind Exclusions during trial: 4 in Rx group (survival status known for all except one) Losses to FU: 2 in Rx group
Participants	Hong Kong 312 participants Mean age 67 years 58% male 100% CT before entry Ischaemic stroke with motor deficit Less than 48 hours since stroke onset
Interventions	Rx: nadroparin (LMWH) sc (randomised between 4100 anti-Xa units 12 hourly versus 24 hourly) Control: placebo Duration: 10 days All surviving participants received aspirin 100 mg/day after 10 days
Outcomes	Death plus cause of death Functional outcome (dependency assessed using International Stroke Trial simple questions) PE (symptomatic) Intracranial haemorrhage (symptomatic and systematic CT) Recurrent stroke Major extracranial haemorrhage Myocardial infarction
Notes	Ex: over 80 years, BP > 180/120 mmHg, previous disabling stroke, bleeding risk, imminent death FU: 6 months

Risk of bias

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

FISS-bis 1998

Methods	C = sequentially numbered boxes Doctor, patient and assessor blind Exclusions during trial: unknown Losses to FU: unknown
Participants	International 766 participants Mean age unknown % male unknown

FISS-bis 1998 *(Continued)*

	100% CT before entry Ischaemic stroke with motor deficit < 24 hours since stroke onset
Interventions	Rx: nadroparin (LMWH) 86 units/kg sc once daily versus 86 units/kg sc 12 hourly Control: placebo Duration: 10 days
Outcomes	Death Functional Outcome (Barthel Index score < 85 = dependent) Intracerebral haemorrhage (symptomatic CT)
Notes	Ex: mild stroke, coma FU: 6 months

Risk of bias

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

IST 1997

Methods	C = telephone randomisation Unblinded; dependency assessment mainly blinded Exclusions during trial: none Losses to FU: data 99.99% complete for 14-day outcome and 99.2% complete for 6-month outcome
Participants	International 19,435 participants 61% > 70 years 54% male 67% CT prior to randomisation, 29% CT after randomisation Ischaemic stroke < 48 hours since stroke onset
Interventions	Rx: sc heparin (5000 IU or 12,500 IU 12 hourly), aspirin 300 mg, both, or neither (factorial design) Duration: 14 days or until discharge from hospital
Outcomes	Death Functional outcome (validated simple questions) Recurrent stroke PE Intracranial haemorrhage (symptomatic CT) Extracranial haemorrhage
Notes	Ex: small likelihood of worthwhile benefit; high risk of adverse effect (e.g. hypersensitivity of aspirin, recent GI bleed or peptic ulcer disease, already on long-term anticoagulation) FU: 6 months

Risk of bias

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

Kwiecinski 1995

Methods	C = unknown Blinding not stated Exclusions during trial: unknown Losses to FU: unknown
Participants	Poland 120 participants Mean age 57 years 65% male 100% CT before entry Enrolled less than 48 hours after ischaemic stroke
Interventions	Rx: fraxiparin (LMWH) 0.6 ml 12 hourly for one week, then 0.3ml 12 hourly for one week Control: placebo Duration: 14 days
Outcomes	Death Functional outcome Intracerebral haemorrhage (symptomatic CT) Symptomatic DVT and PE during treatment period
Notes	Ex: > 65 years, comatose, severe comorbidity, uncontrolled hypertension FU: 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Marshall 1960

Methods	C = unknown Non-blind Exclusions during trial: none Losses to FU: none
Participants	United Kingdom 51 participants 30 to 70 years 47% male No CT, 100% LP plus angiography Non-cardioembolic ischaemic stroke < 72 hours since stroke onset
Interventions	Rx: heparin iv (3 doses of 12,500 IU), then phenindione orally 12 hourly (PT 2 to 3) Control: no treatment Duration: 21 days No antiplatelet therapy during follow up
Outcomes	Death but not cause of death Fatal intracranial haemorrhage (autopsies in 8/9 deaths) Recurrent stroke

Marshall 1960 *(Continued)*

	Major extracranial haemorrhage
Notes	Ex: bleeding risk FU: 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

McCarthy 1977

Methods	C = sealed envelopes (? opaque and sequentially numbered) DVT assessment blind Exclusions during trial: none Losses to FU: none
Participants	United Kingdom 32 participants Mean age 78 years 34% male No CT, 100% LP before entry Any stroke with no blood in CSF Less than 48 hours since stroke onset
Interventions	Rx: heparin 5000 IU sc 8 hourly Control: no treatment Duration: 14 days
Outcomes	Death but not cause of death DVT (systematic I-125 scan)
Notes	Ex: BP > 120 diastolic, bleeding risk FU: 1 month

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

McCarthy 1986

Methods	C = sealed envelopes (? opaque and sequentially numbered) DVT assessment blind Exclusions during trial: none Losses to FU: none
Participants	United Kingdom 305 participants Mean age 76 years

McCarthy 1986 *(Continued)*

	43% male No CT before entry All strokes (10% haemorrhagic on autopsy) Less than 48 hours since stroke onset
Interventions	Rx: heparin 5000 IU sc 8 hourly Control: no treatment Duration: 14 days Antiplatelet therapy during follow up not reported
Outcomes	Death but not cause of death DVT (systematic I-125 scan)
Notes	Ex: BP > 120 diastolic, bleeding risk FU: 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

NAT-COOP 1962

Methods	C = sealed envelopes (? opaque and sequentially numbered) Patient only blind Exclusions during trial: none Losses to FU: none
Participants	USA 30 participants 26 older than 55 years 53% male No CT, 100% LP before entry Cardioembolic stroke Less than 2 weeks since stroke onset
Interventions	Rx: heparin 50 mg iv 4 hourly, then dicumarol (oral anticoagulant; PT 15 to 20%) Control: placebo Duration: 1 month
Outcomes	Death plus cause of death Recurrent stroke Extracranial haemorrhage
Notes	Ex: bleeding risk FU: 1 year but only complete FU for all patients up to 1 month

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Pambianco 1995

Methods	C = sealed, opaque but not sequentially numbered envelopes Non-blind Exclusions during trial: none Losses to FU: none
Participants	USA 131 participants Mean age 71 years 50% male 100% CT before entry Ischaemic stroke with severe leg weakness Less than 14 days since stroke onset
Interventions	Rx: heparin 5000 IU sc 8 hourly, with dose adjustment to maintain PT 30 to 40 seconds Control: no treatment Duration: 28 days
Outcomes	Death plus cause of death DVT (systematic B mode and Doppler ultrasound) PE Major extracranial haemorrhage
Notes	Ex: bleeding risk, active cancer FU: 28 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Pince 1981

Methods	C = sealed envelopes (? opaque and sequentially numbered) Non-blind Exclusions during trial: Rx 0, control 4 participants (2 with intracranial haemorrhage) Losses to FU: none
Participants	France 80 participants 30 to 92 years 62% male No CT, 100% LP before entry Ischaemic stroke affecting the leg Less than 7 days since stroke onset (89% < 48 hours)
Interventions	Rx: heparin 5000 IU sc 8 hourly Control: no treatment Duration: 10 days
Outcomes	Death but not cause of death DVT (systematic I-125 scan) PE

Pince 1981 *(Continued)*

	Major extracranial haemorrhage
Notes	Ex: bleeding risk FU: 10 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Prins 1989

Methods	C = sequentially numbered identical syringes Double-blind Exclusions during trial: none Losses to FU: none
Participants	Netherlands 60 participants 78% > 70 years 52% male 100% CT before entry Ischaemic stroke less than 72 hours since stroke onset
Interventions	Rx: dalteparin (LMWH, Kabi 2165) 2500 anti-Xa units sc 12 hourly Control: placebo Duration: 14 days
Outcomes	Death plus cause of death DVT (systematic I-125 scan with venography) PE Intracranial haemorrhage (symptomatic plus systematic CT) Major extracranial haemorrhage
Notes	Ex: coma FU: 14 days

Risk of bias

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

Sandset 1990

Methods	C = sequentially numbered identical ampoules Doctor, patient and assessor blind Exclusions during trial: none Losses to FU: none
Participants	Norway

Sandset 1990 *(Continued)*

	103 participants 47 to 90 years 45% male 100% CT before entry Non-cardioembolic ischaemic stroke Less than 72 hours since stroke onset
Interventions	Rx: dalteparin (LMWH, Kabi 2165) 3000 to 5500 anti-Xa U sc 24 hourly Control: placebo Duration: 14 days
Outcomes	Death plus cause of death DVT (systematic venography or B mode ultrasound) PE (symptomatic plus autopsy in 5/6 deaths) Intracranial haemorrhage (systematic CT) Major extracranial haemorrhage
Notes	Ex: BP > 120 diastolic, coma, bleeding risk FU: 28 days

Risk of bias

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

Tazaki 1986

Methods	C = numbered or coded containers administered sequentially to enrolled participants Doctor, patient and assessor blind Exclusions during trial: none Losses to FU: none
Participants	Japanese 156 participants 68% > 60 years 66% male 100% CT before entry Ischaemic stroke within 7 to 10 days of stroke onset
Interventions	Rx: MD805 (thrombin inhibitor) 60 mg/day versus 30 mg/day continuous iv for 2 days; then 20 mg 12 hourly iv for 5 days Control: placebo All patients received glycerol 500 mg/day Duration: 7 days
Outcomes	Death Functional outcome (graded on ADL-type scale)
Notes	Ex: decreased level of consciousness, pregnancy, 'bleeding tendency', severe hepatic or renal damage FU: 28 days

Risk of bias

Bias	Authors' judgement	Support for judgement

Tazaki 1986 *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Tazaki 1992

Methods	C = numbered or coded containers administered sequentially to enrolled patients Doctor, patient and assessor blind Exclusions during trial: none Losses to FU: none
Participants	Japanese 138 participants Mean age 68 years 64% male 100% CT before entry Ischaemic stroke within 5 to 7 days of stroke onset
Interventions	Rx: MD805 (thrombin inhibitor) 60 mg/days for two days (continuous iv), then MD805 20 mg 12 hourly for 5 days (iv) Control: placebo All groups received glycerol 500 ml/day for 7 days Duration: 7 days
Outcomes	Death Functional outcome Intracranial haemorrhage (symptomatic CT)
Notes	Ex: decreased level of consciousness, bleeding risk, pregnancy, age > 85 years, significant medical disease (cardiac, hepatic, renal) FU: 1 month

Risk of bias

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

TOAST 1998

Methods	C = permuted blocks with randomly ordered sizes of 6, 6, and 4; randomisation lists pharmacy controlled Doctor, patient and assessor blind Exclusions during trial: none Losses to FU: 25 participants (11 treatment, 14 control)
Participants	United States 1281 participants Mean age 65 years 61% male 100% CT before entry Ischaemic stroke > 1 hour and < 24 hours from symptom onset with estimated pre-stroke Barthel Index or 12 or more

TOAST 1998 *(Continued)*

Interventions	Rx: danaparoid (heparinoid Org 10172) bolus followed by continuous infusion to maintain blood anti-Xa levels of 0.6 to 0.8 Control: placebo Duration: 7 days
Outcomes	Functional outcome: Barthel Index < 85, NIHSS, Glasgow Outcome Scale Recurrent stroke Intracranial haemorrhage (symptomatic CT) Extracranial haemorrhage
Notes	Ex: Age < 18 or > 85, women of childbearing potential, severe stroke (NIHSS score > 15), weight less than 125 pounds FU: 7 days and 3 months

Risk of bias

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

Turpie 1987

Methods	C = sequentially numbered identical containers Double-blind Exclusions during trial: none Losses to FU: none
Participants	Canada 75 participants 28 to 90 years 53% male 100% CT before entry Non-cardioembolic ischaemic stroke with immobility Less than 7 days since stroke onset
Interventions	Rx: danaparoid (heparinoid Org 10172) 750 anti-Xa units sc 12 hourly Control: placebo Duration: 14 days or prior discharge Antiplatelet therapy during follow up not reported
Outcomes	Death plus cause of death DVT (systematic I-125 scan + plethysmography with venography) PE (symptomatic) Intracranial haemorrhage (symptomatic CT) Extracranial haemorrhage Recurrent stroke
Notes	Ex: bleeding risk FU: 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement

Turpie 1987 *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Vissinger 1995

Methods	C = coded containers administered sequentially to enrolled participants Doctor, patient and assessor blind Exclusions during trial: none Losses to FU: 31/50 participants lost to 6-month follow up
Participants	Denmark 50 participants Mean age 71.8 years 58% male 66% CT before entry - haemorrhage excluded in remainder by cerebral scintigraphy Non-embolic ischaemic stroke with motor deficit < 24 hours since stroke onset
Interventions	Rx: tinzaparin (LMWH) 3500 anti-Xa IU sc once daily Control: placebo Duration: 14 days or until full mobilisation
Outcomes	Death DVT (venography) PE (symptomatic)
Notes	Exclusion criteria: < 50 years old, hypertension (BP > 200/120 mmHg), coma, aphasia, bleeding risk, oral anticoagulant treatment, severe hepatic or renal disease, clinical suspicion of DVT or PE FU: 12 to 14 days and 6 months

Risk of bias

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

ADL: activities of daily living
APTT: activated partial thromboplastin time
bid: twice a day
BP: blood pressure
C: concealment of allocation
CSF: cerebrospinal fluid
CT: computerised tomography
DVT: Deep venous thrombosis
Ex: exclusion criteria
FU: follow up
GI: gastrointestinal
ICH: intracranial haemorrhage
im: intramuscularly
iv: intravenous, intravenously
LMWH: low-molecular-weight heparin
LP: lumbar puncture
MRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
OHS: Oxford Handicap Score
PE: pulmonary embolism

PT: prothrombin time
Rx: treatment
sc: subcutaneous, subcutaneously

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

Study	Reason for exclusion
Bradshaw 1975	Non-random: allocation by odd/even year of birth
Camerlingo 2005	Confounded by the use of low-dose unfractionated heparin in control group
Carter 1961	Non-random: alternate allocation
COU 9116	Participants randomised after 14 days of stroke onset
Czechanowski 1981	Confounded with dihydroergotamine
Dahan 1986	Not all participants were stroke patients: individual patient data for stroke patients not available
Dan 2001	Methods of randomisation unclear; no clinically relevant outcomes reported
Dehen 1994	Control group received a low-molecular-weight heparin i.e. dermatan sulphate plus placebo versus low-molecular-weight heparin plus placebo
Enger 1965	Time from stroke to treatment unclear
Eriksson 1983	Non-random: allocation by month of admission
Gelmers 1980	Non-random: alternate allocation
Kang 2010	No clinical outcome data
Kario 1995	No clinically relevant outcomes reported
Kobayashi 1997	No clinically relevant outcomes reported
Lee 1994	Confounded with urokinase
Lee 2008	Comparison of 2 anticoagulant regimens
Luo 2013	Comparison of 2 anticoagulant regimens
McCarthy 1993	Data not available despite repeated contact with authors
McDevitt 1959	Time from stroke to treatment unclear
Meredit 2009	Comparison of 2 anticoagulant regimens
Rosin 1994	Data not available despite repeated contact with authors
Shi 2004	No clinically relevant outcomes reported
Stiekema 1988	No control group: dose-finding trial
Tan 1998	Not randomised; no clinically relevant outcomes reported

Study	Reason for exclusion
Thygesen 1964	Non-random allocation
Tomek 2011	Comparison of 2 anticoagulant regimens
Tsuchiya 1989	Confounded with urokinase
Tsuchiya 1990	Confounded with urokinase
VA Study 1961	Treatment started acutely in only 50% and unable to get individual patient data for just these participants
Zhang 2005	Not clearly randomised
Zhao 2014	Anticoagulant versus antiplatelet regimen

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

Nosal 2014

Trial name or title	Safety and efficacy of heparin and nadroparin in the acute phase of ischemic stroke (Heparinas)
Methods	Double Blind (patient, caregiver, investigator, outcomes assessor)
Participants	18 to 80 years old Estimated 150 participants Slovakia
Interventions	Rx: heparin iv/nadroparin sc/placebo iv immediately Followed by nadroparin sc at 24 hours Duration of anticoagulation: 72 hours
Outcomes	Safety: incidence of intracranial haemorrhage Efficacy: level of improvement measured by mRS, and NIHSS
Starting date	May 2013
Contact information	Vladimir Nosal, MD, PhD, vnosal@gmail.com
Notes	ClinicalTrials.gov Identifier: NCT01862978

iv: intravenous
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
sc: subcutaneous

DATA AND ANALYSES

Comparison 1. Anticoagulant versus control in acute presumed ischaemic stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dead or dependent at end of follow up (if > 1 month)	8	22125	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.93, 1.04]
1.1 Unfractionated heparin (subcutaneous) versus control	1	19435	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.94, 1.06]
1.2 Low-molecular-weight heparin versus control	4	1228	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.64, 1.04]
1.3 Heparinoid (subcutaneous) versus control	1	57	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.29, 2.27]
1.4 Heparinoid (intravenous) versus control	1	1276	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.72, 1.19]
1.5 Direct thrombin inhibitor versus control (intravenous)	1	129	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.62, 2.62]
2 Death from all causes during treatment period	21	22562	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.90, 1.09]
2.1 Unfractionated heparin (subcutaneous) versus control	5	19743	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.88, 1.07]
2.2 Unfractionated heparin (intravenous) versus control	2	270	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.11, 3.71]
2.3 Low-molecular-weight heparin versus control	6	585	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.60 [0.87, 2.95]
2.4 Heparinoid (subcutaneous) versus control	2	132	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.32, 3.37]
2.5 Heparinoid (intravenous) versus control	1	1281	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.55, 3.11]
2.6 Oral vitamin K antagonist versus control	2	81	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.46, 3.48]
2.7 Thrombin inhibitor versus control	3	470	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.60 [0.95, 7.09]
3 Death from all causes at final follow up (if > 1 month)	11	22776	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.98, 1.12]
3.1 Unfractionated heparin (subcutaneous) versus control	2	19740	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.98, 1.12]
3.2 Unfractionated heparin (intravenous) versus control	1	225	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.26 [0.99, 5.19]
3.3 Low-molecular-weight heparin versus control	4	1228	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.74, 1.32]

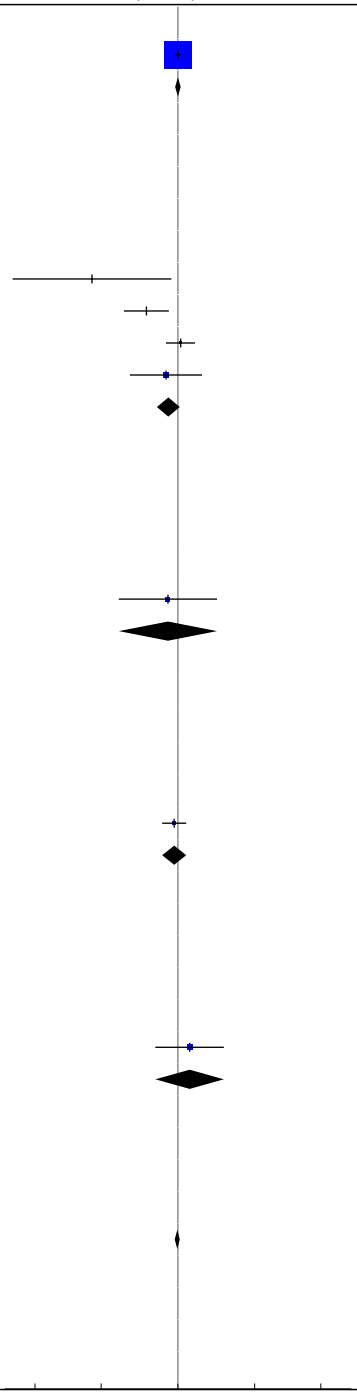
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4 Heparinoid (subcutaneous) versus control	1	75	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.09, 2.05]
3.5 Heparinoid (intravenous) versus control	1	1281	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.69, 1.72]
3.6 Oral vitamin K antagonist versus control	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.14 [0.35, 3.76]
3.7 Direct thrombin inhibitor (intravenous) versus control	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.79 [0.71, 4.53]
4 Deep vein thrombosis during treatment period	10	916	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.21 [0.15, 0.29]
4.1 Unfractionated heparin (subcutaneous) versus control	5	609	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.11, 0.24]
4.2 Low-molecular-weight heparin versus control	4	232	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.23, 0.73]
4.3 Heparinoid (subcutaneous) versus control	1	75	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.11 [0.02, 0.46]
5 Symptomatic pulmonary embolism during treatment period	14	22544	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.44, 0.81]
5.1 Unfractionated heparin (subcutaneous) versus control	3	19645	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.49, 0.96]
5.2 Unfractionated heparin (intravenous) versus control	1	45	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Low-molecular-weight heparin versus control	7	1441	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.31 [0.15, 0.64]
5.4 Heparinoid (subcutaneous) versus control	2	132	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.66 [0.15, 386.16]
5.5 Heparinoid (intravenous) versus control	1	1281	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.70]
6 Recurrent ischaemic or unknown stroke during treatment period	11	21605	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.65, 0.88]
6.1 Unfractionated heparin (subcutaneous) versus control	2	19566	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.65, 0.89]
6.2 Unfractionated heparin (intravenous) versus control	1	45	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.11 [0.01, 1.85]
6.3 Low-molecular-weight heparin versus control	2	362	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.47 [0.14, 1.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.4 Heparinoid (subcutaneous) versus control	2	132	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.48 [0.07, 286.49]
6.5 Heparinoid (intravenous) versus control	1	1281	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.34, 2.82]
6.6 Oral vitamin K antagonist versus control	2	81	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.65 [0.11, 3.90]
6.7 Thrombin inhibitor versus control	1	138	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
7 Symptomatic intracranial haemorrhage during treatment period	16	22943	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.55 [1.95, 3.33]
7.1 Unfractionated heparin (subcutaneous) versus control	3	19631	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.69 [1.97, 3.67]
7.2 Unfractionated heparin (intravenous) versus control	2	270	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Low-molecular-weight heparin versus control	6	1321	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.61 [0.80, 3.22]
7.4 Heparinoid (subcutaneous) versus control	1	75	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.48 [0.07, 286.49]
7.5 Heparinoid (intravenous) versus control	1	1281	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.91 [0.98, 8.69]
7.6 Oral vitamin K antagonist versus control	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.78 [0.37, 21.00]
7.7 Thrombin inhibitor versus control	1	138	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
7.8 Direct thrombin inhibitor (intravenous) versus control	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.60 [0.70, 30.35]
8 Any recurrent stroke or symptomatic intracranial haemorrhage during treatment period or follow up (> 1 month)	11	21605	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.85, 1.11]
8.1 Unfractionated heparin (subcutaneous) versus control	2	19566	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.84, 1.11]
8.2 Unfractionated heparin (intravenous) versus control	1	45	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.11 [0.01, 1.85]
8.3 Low-molecular-weight heparin versus control	2	362	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.39 [0.12, 1.26]
8.4 Heparinoid (subcutaneous) versus control	2	132	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.57 [0.24, 88.28]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.5 Heparinoid (intravenous) versus control	1	1281	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [0.67, 3.07]
8.6 Oral vitamin K antagonist versus control	2	81	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.32, 4.88]
8.7 Thrombin inhibitor versus stroke	1	138	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.61 [0.78, 74.40]
9 Major extracranial haemorrhage during treatment period	18	22255	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.99 [2.24, 3.99]
9.1 Unfractionated heparin (subcutaneous) versus control	4	19711	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.06 [2.25, 4.15]
9.2 Unfractionated heparin (intravenous) versus control	1	45	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Low-molecular-weight heparin versus control	5	535	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.03, 9.05]
9.4 Heparinoid (subcutaneous) versus control	2	132	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.66 [0.15, 386.16]
9.5 Heparinoid (intravenous) versus control	1	1281	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.31 [1.20, 9.15]
9.6 Oral vitamin K antagonist versus control	2	81	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]
9.7 Thrombin inhibitor versus control	2	294	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.8 Direct thrombin inhibitor (intravenous) versus control	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Subgroup analysis by anticoagulant dose: effect on death or dependency	8	22127	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.93, 1.04]
10.1 Adjusted full-dose intravenous anticoagulant	2	1409	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.75, 1.20]
10.2 Medium fixed-dose anticoagulant	4	10361	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.91, 1.06]
10.3 Low fixed-dose anticoagulant	5	10357	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.92, 1.08]

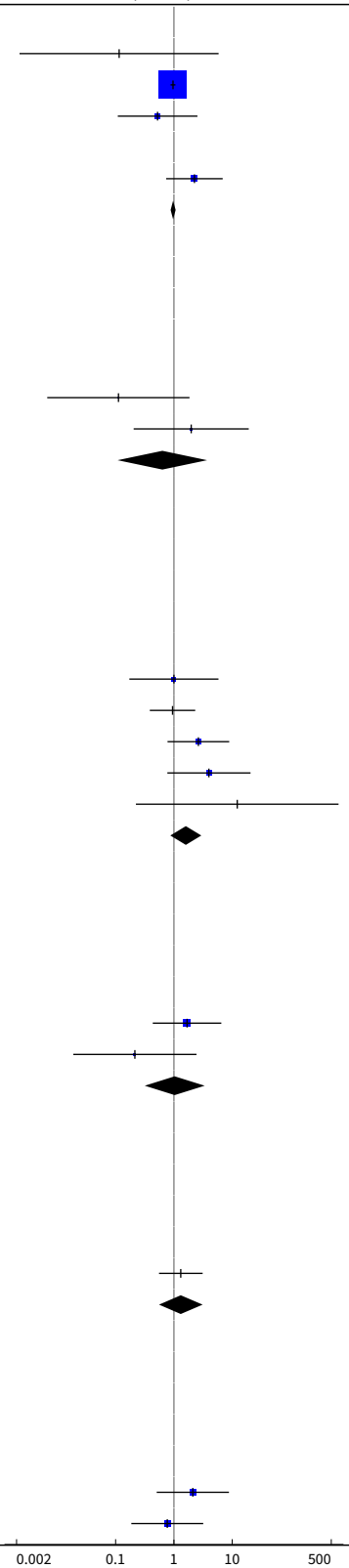
Analysis 1.1. Comparison 1 Anticoagulant versus control in acute presumed ischaemic stroke, Outcome 1 Dead or dependent at end of follow up (if > 1 month).

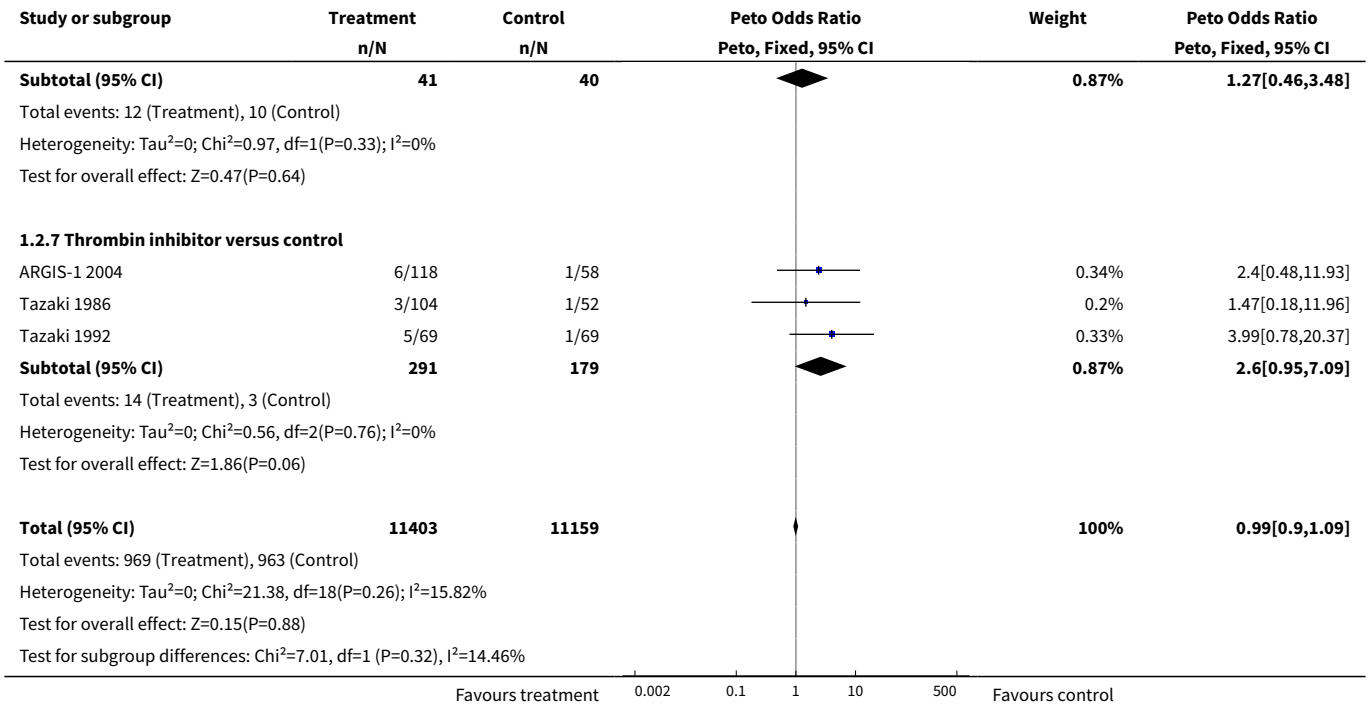
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 Unfractionated heparin (subcutaneous) versus control					
IST 1997	6063/9717	6062/9718		89.17%	1[0.94,1.06]
Subtotal (95% CI)	**9717**	**9718**		**89.17%**	**1[0.94,1.06]**
Total events: 6063 (Treatment), 6062 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.02(P=0.98)					
1.1.2 Low-molecular-weight heparin versus control					
Chaudhary 2002	1/15	6/15		0.11%	0.17[0.03,0.87]
FISS 1995	100/207	68/105		1.36%	0.52[0.32,0.83]
FISS-bis 1998	300/516	142/250		3.22%	1.06[0.78,1.43]
Kwiecinski 1995	19/62	21/58		0.53%	0.78[0.37,1.66]
Subtotal (95% CI)	**800**	**428**		**5.21%**	**0.82[0.64,1.04]**
Total events: 420 (Treatment), 237 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.92, df=3(P=0.02); I^2=69.76%					
Test for overall effect: Z=1.64(P=0.1)					
1.1.3 Heparinoid (subcutaneous) versus control					
Cazzato 1989	13/28	15/29		0.28%	0.81[0.29,2.27]
Subtotal (95% CI)	**28**	**29**		**0.28%**	**0.81[0.29,2.27]**
Total events: 13 (Treatment), 15 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.4(P=0.69)					
1.1.4 Heparinoid (intravenous) versus control					
TOAST 1998	159/641	167/635		4.75%	0.92[0.72,1.19]
Subtotal (95% CI)	**641**	**635**		**4.75%**	**0.92[0.72,1.19]**
Total events: 159 (Treatment), 167 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.61(P=0.54)					
1.1.5 Direct thrombin inhibitor versus control (intravenous)					
ARGIS-1 2004	43/83	21/46		0.58%	1.28[0.62,2.62]
Subtotal (95% CI)	**83**	**46**		**0.58%**	**1.28[0.62,2.62]**
Total events: 43 (Treatment), 21 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
Total (95% CI)	**11269**	**10856**		**100%**	**0.99[0.93,1.04]**
Total events: 6698 (Treatment), 6502 (Control)					
Heterogeneity: Tau^2=0; Chi^2=13.37, df=7(P=0.06); I^2=47.66%					
Test for overall effect: Z=0.45(P=0.65)					
Test for subgroup differences: Chi^2=3.45, df=1 (P=0.48), I^2=0%					



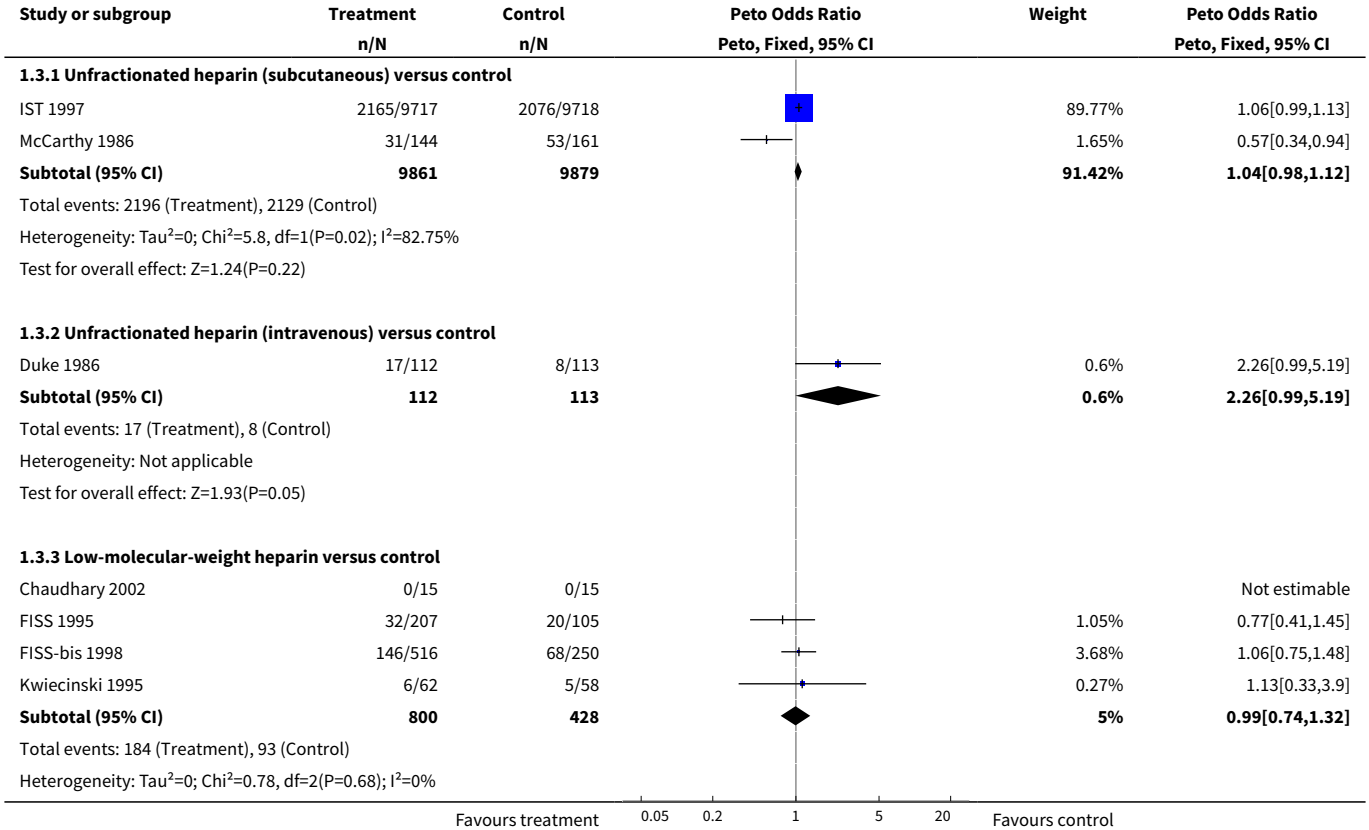
Analysis 1.2. Comparison 1 Anticoagulant versus control in acute presumed ischaemic stroke, Outcome 2 Death from all causes during treatment period.

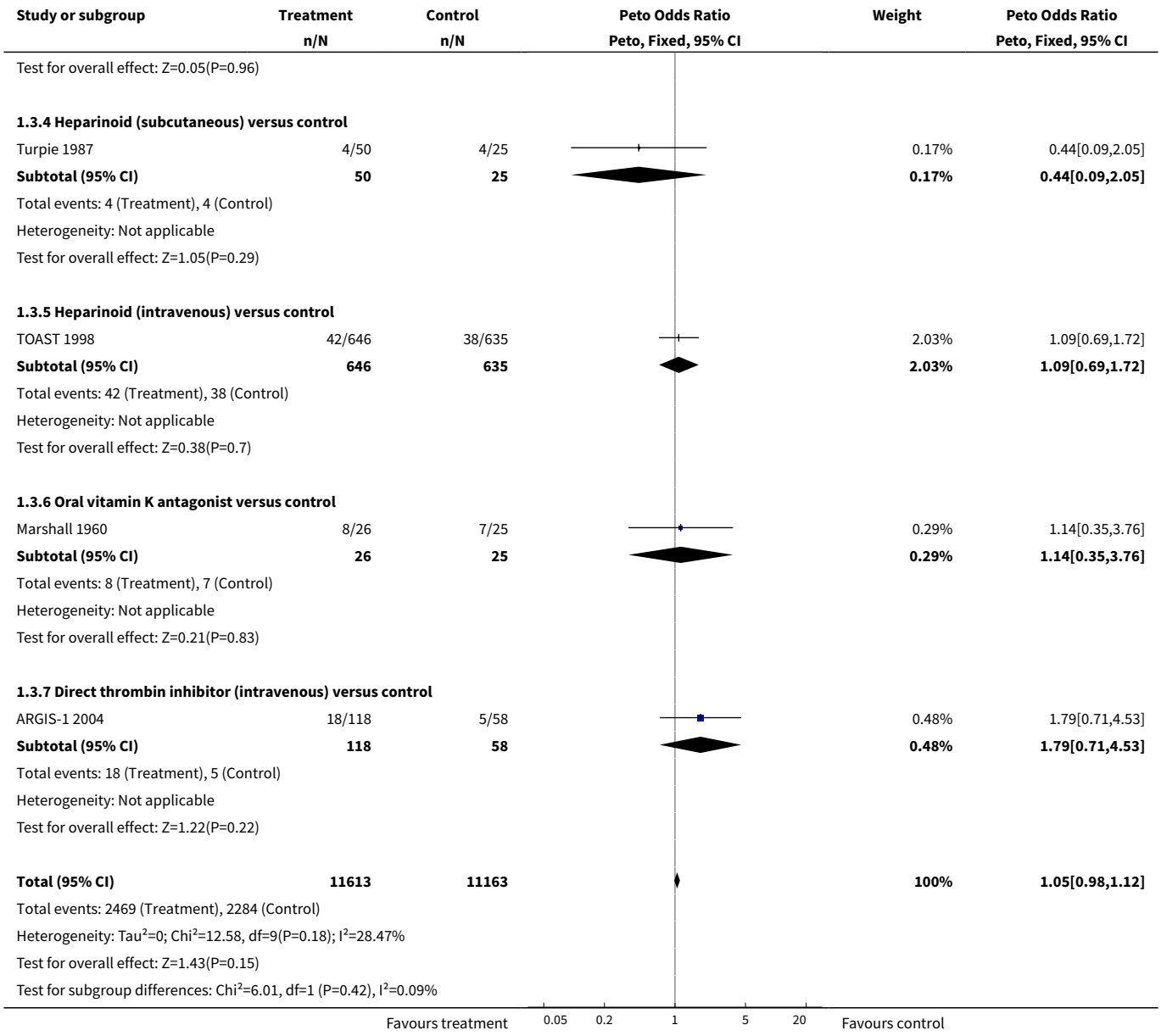
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.2.1 Unfractionated heparin (subcutaneous) versus control					
Duke 1983	0/35	1/30		0.06%	0.11[0,5.84]
IST 1997	876/9717	905/9718		92.69%	0.96[0.88,1.06]
McCarthy 1977	3/16	5/16		0.35%	0.52[0.11,2.53]
Pambianco 1995	0/64	0/67			Not estimable
Pince 1981	10/40	5/40		0.71%	2.25[0.74,6.86]
Subtotal (95% CI)	**9872**	**9871**		**93.81%**	**0.97[0.88,1.07]**
Total events: 889 (Treatment), 916 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.91, df=3(P=0.27); I^2=23.27%					
Test for overall effect: Z=0.67(P=0.5)					
1.2.2 Unfractionated heparin (intravenous) versus control					
CESG 1983	0/24	2/21		0.11%	0.11[0.01,1.85]
Duke 1986	2/112	1/113		0.17%	1.98[0.2,19.2]
Subtotal (95% CI)	**136**	**134**		**0.28%**	**0.63[0.11,3.71]**
Total events: 2 (Treatment), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.43, df=1(P=0.12); I^2=58.83%					
Test for overall effect: Z=0.5(P=0.61)					
1.2.3 Low-molecular-weight heparin versus control					
Chaudhary 2002	0/15	0/15			Not estimable
Elias 1990	3/15	3/15		0.28%	1[0.17,5.81]
FISS 1995	15/207	8/105		1.09%	0.95[0.39,2.32]
Prins 1989	9/30	4/30		0.59%	2.63[0.78,8.88]
Sandset 1990	5/52	1/51		0.33%	3.98[0.77,20.55]
Vissinger 1995	1/20	0/30		0.05%	12.18[0.22,665.65]
Subtotal (95% CI)	**339**	**246**		**2.35%**	**1.6[0.87,2.95]**
Total events: 33 (Treatment), 16 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.4, df=4(P=0.35); I^2=9.03%					
Test for overall effect: Z=1.5(P=0.13)					
1.2.4 Heparinoid (subcutaneous) versus control					
Cazzato 1989	6/28	4/29		0.48%	1.68[0.43,6.5]
Turpie 1987	1/50	2/25		0.15%	0.21[0.02,2.44]
Subtotal (95% CI)	**78**	**54**		**0.63%**	**1.03[0.32,3.37]**
Total events: 7 (Treatment), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.1, df=1(P=0.15); I^2=52.45%					
Test for overall effect: Z=0.05(P=0.96)					
1.2.5 Heparinoid (intravenous) versus control					
TOAST 1998	12/646	9/635		1.18%	1.31[0.55,3.11]
Subtotal (95% CI)	**646**	**635**		**1.18%**	**1.31[0.55,3.11]**
Total events: 12 (Treatment), 9 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.62(P=0.54)					
1.2.6 Oral vitamin K antagonist versus control					
Marshall 1960	6/26	3/25		0.43%	2.11[0.51,8.79]
NAT-COOP 1962	6/15	7/15		0.44%	0.77[0.19,3.18]



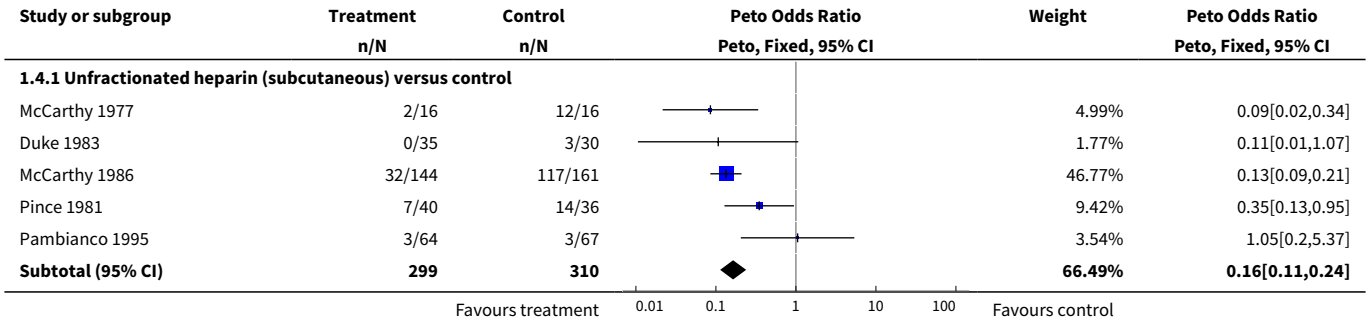


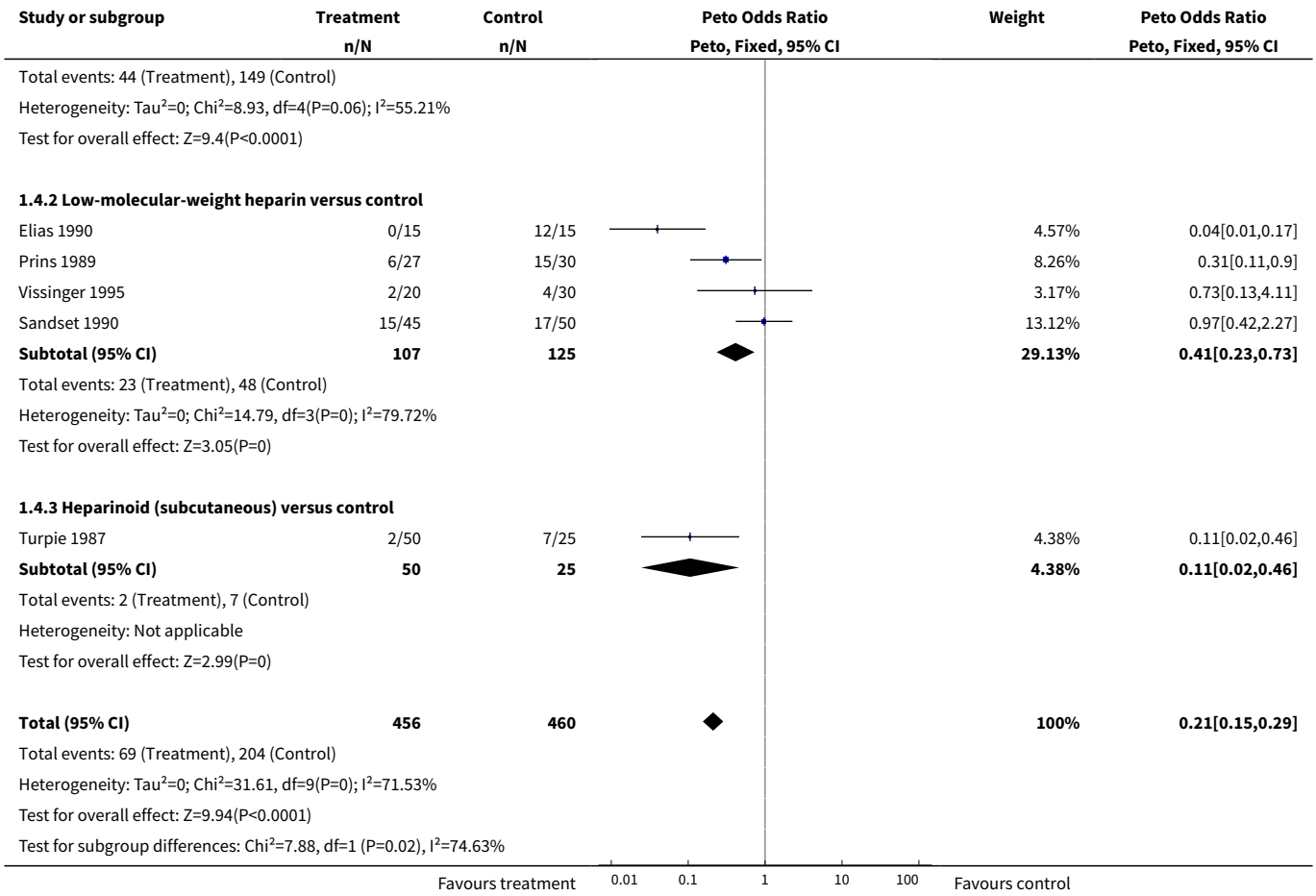
Analysis 1.3. Comparison 1 Anticoagulant versus control in acute presumed ischaemic stroke, Outcome 3 Death from all causes at final follow up (if > 1 month).



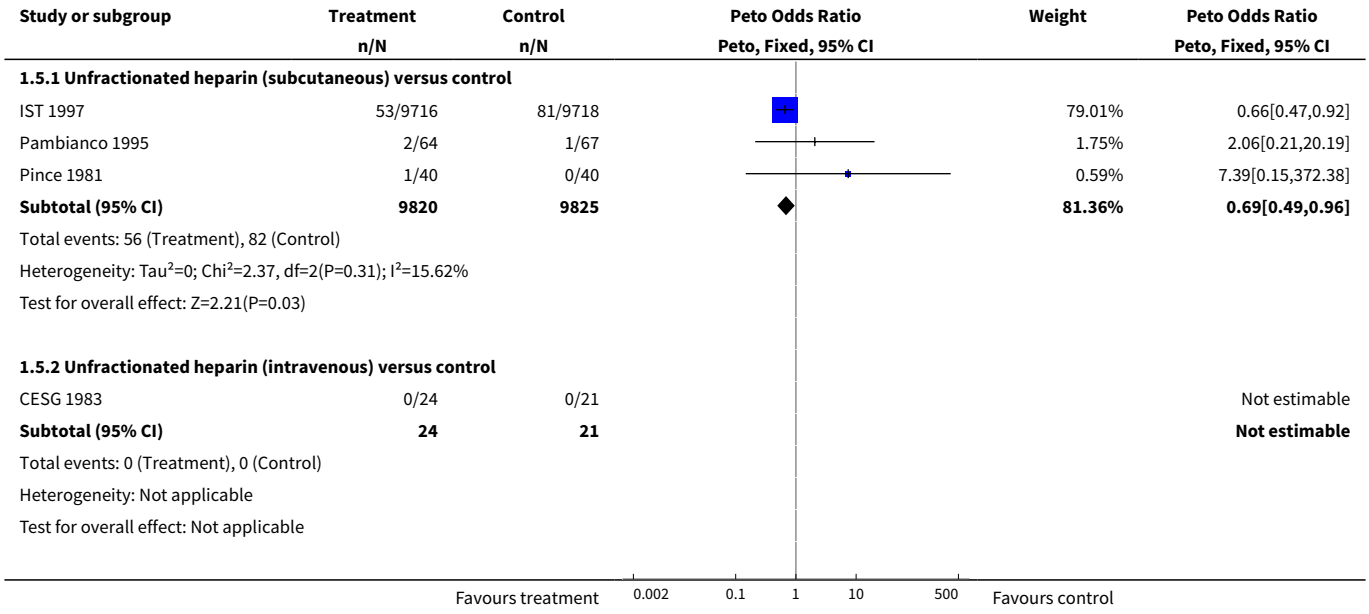


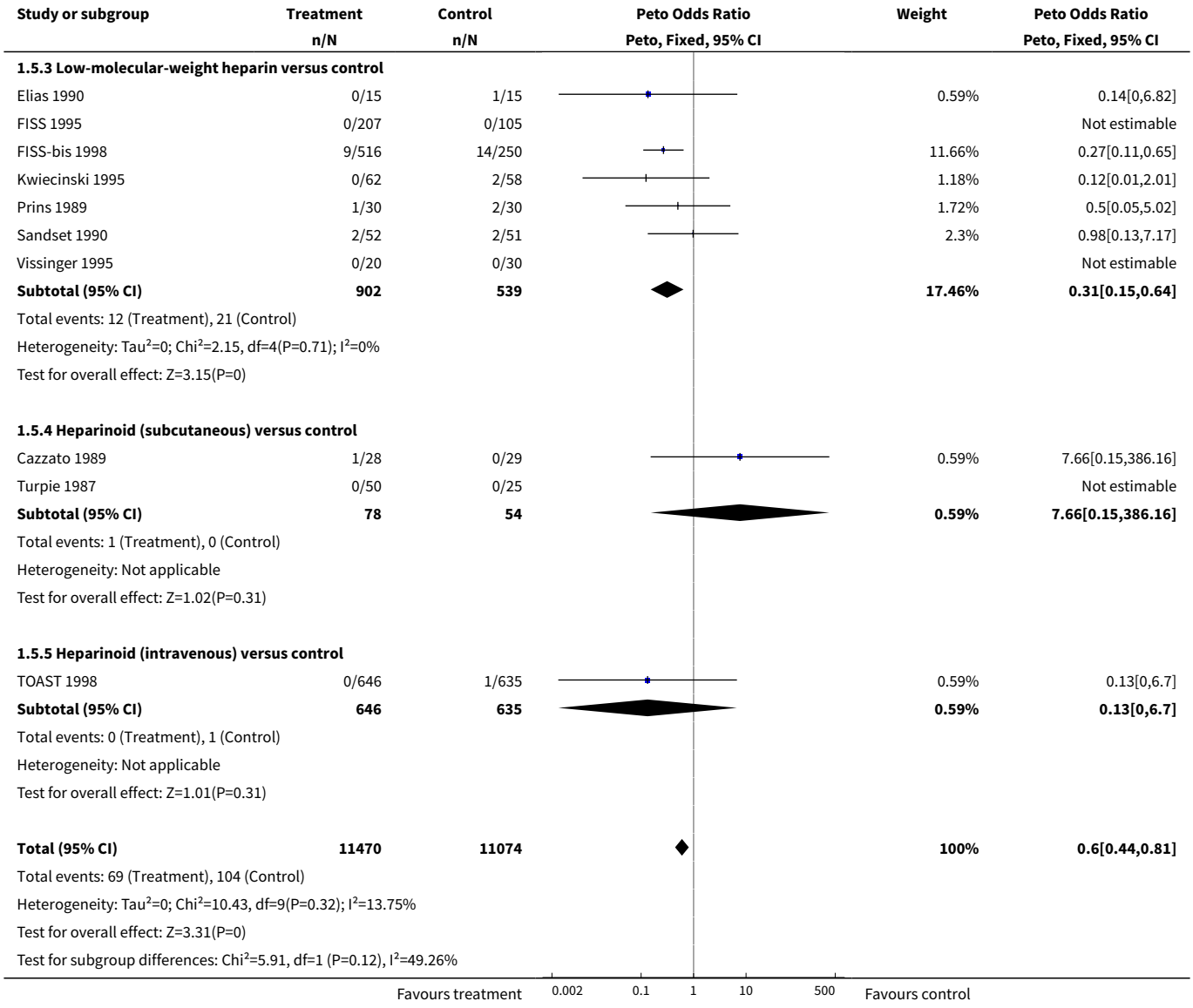
Analysis 1.4. Comparison 1 Anticoagulant versus control in acute presumed ischaemic stroke, Outcome 4 Deep vein thrombosis during treatment period.



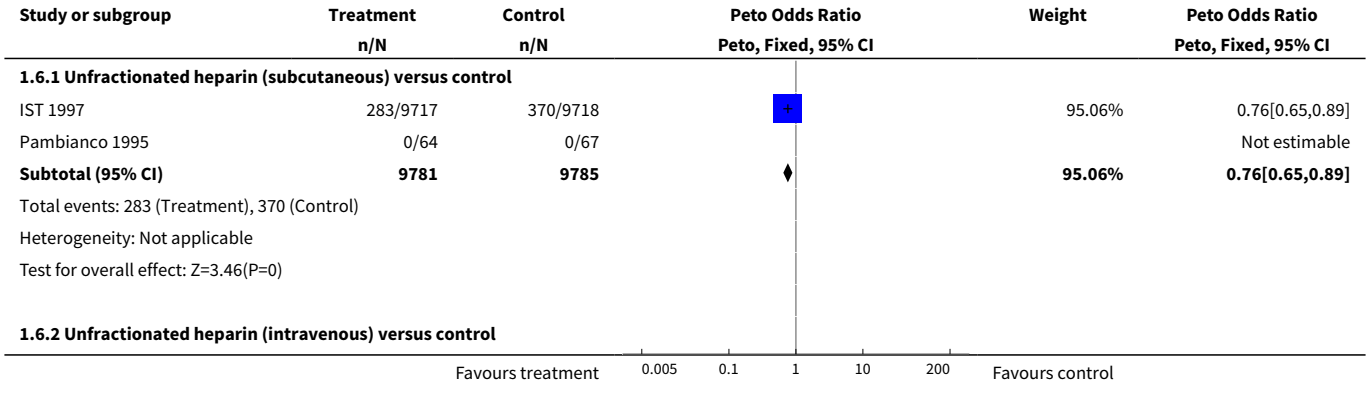


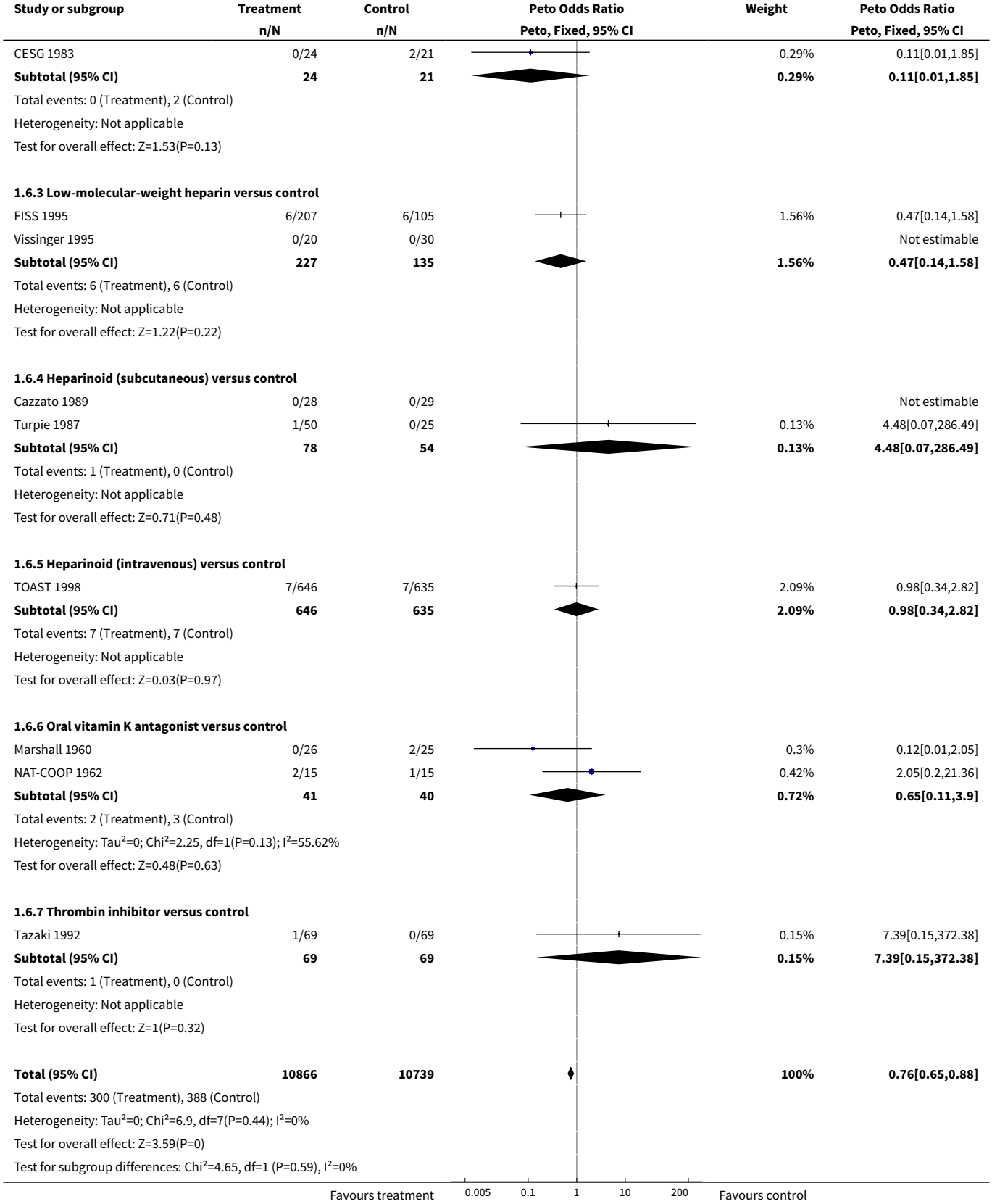
Analysis 1.5. Comparison 1 Anticoagulant versus control in acute presumed ischaemic stroke, Outcome 5 Symptomatic pulmonary embolism during treatment period.





Analysis 1.6. Comparison 1 Anticoagulant versus control in acute presumed ischaemic stroke, Outcome 6 Recurrent ischaemic or unknown stroke during treatment period.

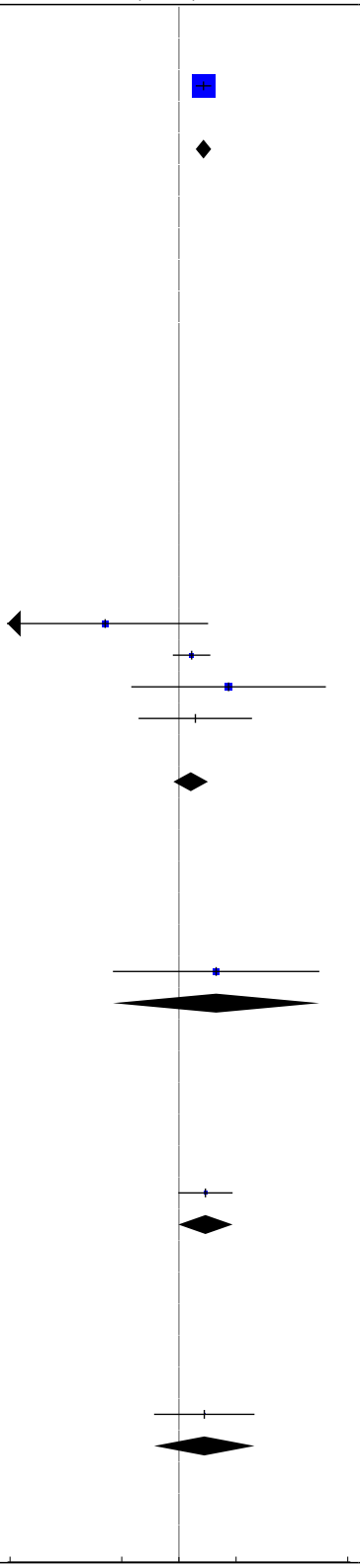


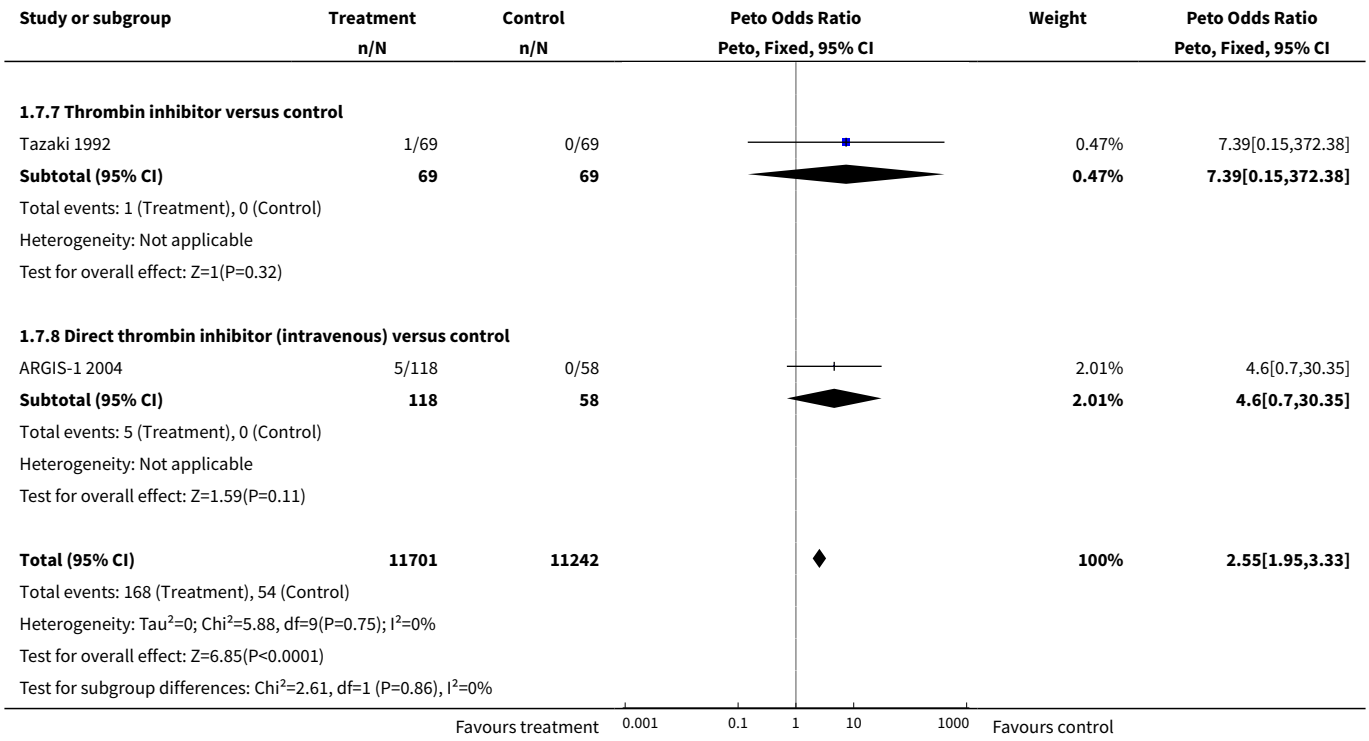


Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
CESG 1983	0/24	2/21		0.29%	0.11[0.01,1.85]
Subtotal (95% CI)	**24**	**21**		**0.29%**	**0.11[0.01,1.85]**
Total events: 0 (Treatment), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.53(P=0.13)					
1.6.3 Low-molecular-weight heparin versus control					
FISS 1995	6/207	6/105		1.56%	0.47[0.14,1.58]
Vissinger 1995	0/20	0/30			Not estimable
Subtotal (95% CI)	**227**	**135**		**1.56%**	**0.47[0.14,1.58]**
Total events: 6 (Treatment), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.22(P=0.22)					
1.6.4 Heparinoid (subcutaneous) versus control					
Cazzato 1989	0/28	0/29			Not estimable
Turpie 1987	1/50	0/25		0.13%	4.48[0.07,286.49]
Subtotal (95% CI)	**78**	**54**		**0.13%**	**4.48[0.07,286.49]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					
1.6.5 Heparinoid (intravenous) versus control					
TOAST 1998	7/646	7/635		2.09%	0.98[0.34,2.82]
Subtotal (95% CI)	**646**	**635**		**2.09%**	**0.98[0.34,2.82]**
Total events: 7 (Treatment), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.03(P=0.97)					
1.6.6 Oral vitamin K antagonist versus control					
Marshall 1960	0/26	2/25		0.3%	0.12[0.01,2.05]
NAT-COOP 1962	2/15	1/15		0.42%	2.05[0.2,21.36]
Subtotal (95% CI)	**41**	**40**		**0.72%**	**0.65[0.11,3.9]**
Total events: 2 (Treatment), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.25, df=1(P=0.13); I^2=55.62%					
Test for overall effect: Z=0.48(P=0.63)					
1.6.7 Thrombin inhibitor versus control					
Tazaki 1992	1/69	0/69		0.15%	7.39[0.15,372.38]
Subtotal (95% CI)	**69**	**69**		**0.15%**	**7.39[0.15,372.38]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1(P=0.32)					
Total (95% CI)	**10866**	**10739**		**100%**	**0.76[0.65,0.88]**
Total events: 300 (Treatment), 388 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.9, df=7(P=0.44); I^2=0%					
Test for overall effect: Z=3.59(P=0)					
Test for subgroup differences: Chi^2=4.65, df=1 (P=0.59), I^2=0%					

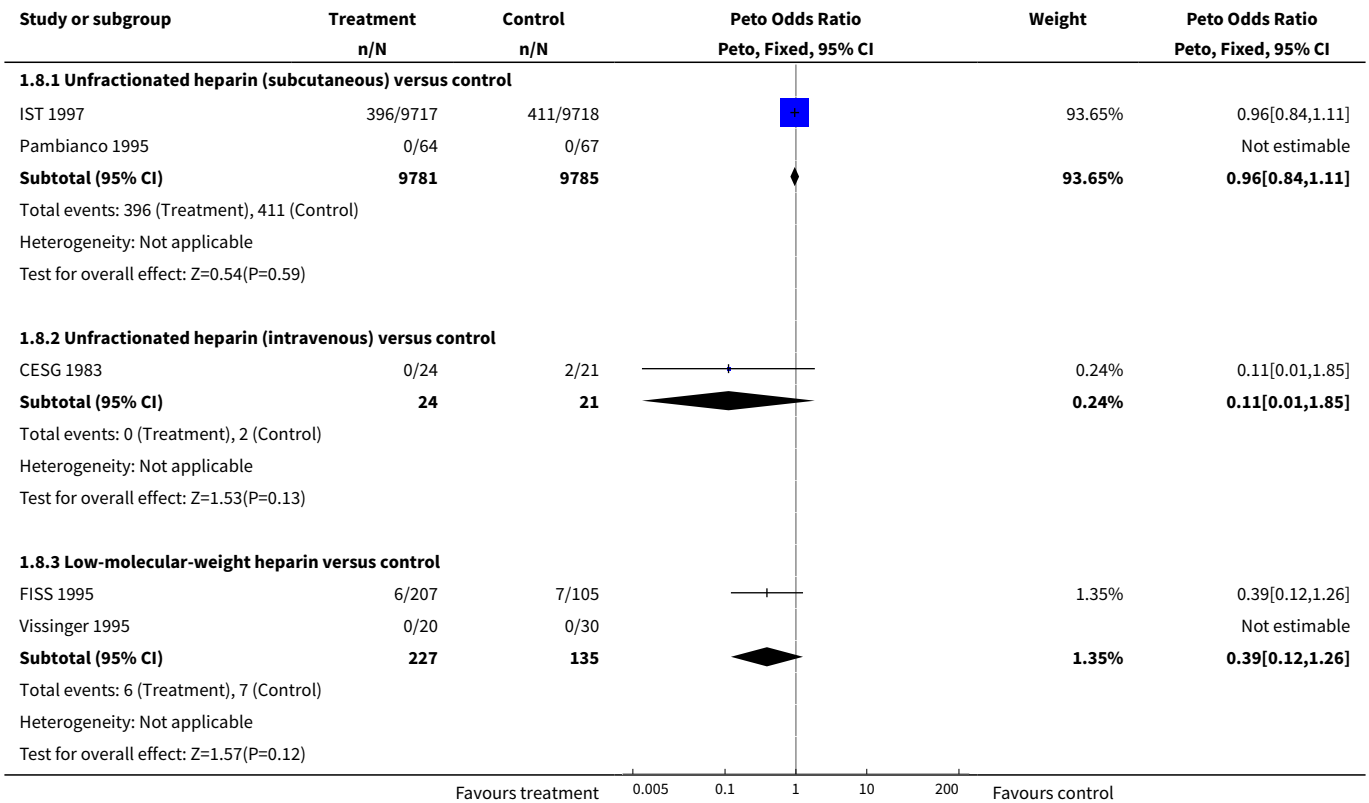
Analysis 1.7. Comparison 1 Anticoagulant versus control in acute presumed ischaemic stroke, Outcome 7 Symptomatic intracranial haemorrhage during treatment period.

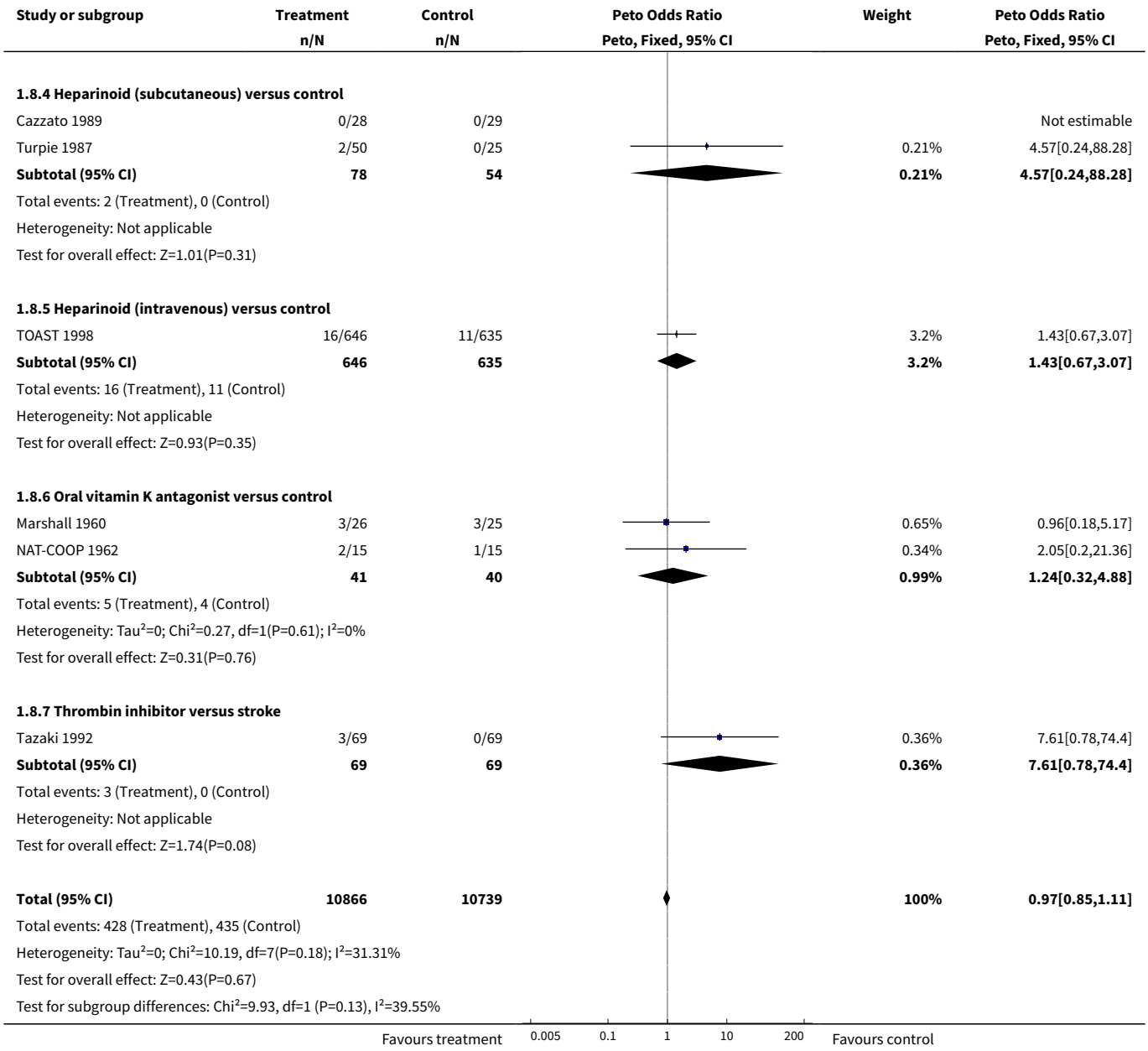
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.7.1 Unfractionated heparin (subcutaneous) versus control					
Duke 1983	0/35	0/30			Not estimable
IST 1997	120/9717	41/9718		74.49%	2.69[1.97,3.67]
Pambianco 1995	0/64	0/67			Not estimable
Subtotal (95% CI)	**9816**	**9815**		**74.49%**	**2.69[1.97,3.67]**
Total events: 120 (Treatment), 41 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=6.25(P<0.0001)					
1.7.2 Unfractionated heparin (intravenous) versus control					
CESG 1983	0/24	0/21			Not estimable
Duke 1986	0/112	0/113			Not estimable
Subtotal (95% CI)	**136**	**134**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.7.3 Low-molecular-weight heparin versus control					
Chaudhary 2002	0/15	0/15			Not estimable
FISS 1995	0/207	1/105		0.42%	0.05[0,3.24]
FISS-bis 1998	25/516	7/250		12.6%	1.67[0.78,3.54]
Prins 1989	1/30	0/30		0.47%	7.39[0.15,372.38]
Sandset 1990	2/52	1/51		1.37%	1.94[0.2,19.03]
Vissinger 1995	0/20	0/30			Not estimable
Subtotal (95% CI)	**840**	**481**		**14.85%**	**1.61[0.8,3.22]**
Total events: 28 (Treatment), 9 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.27, df=3(P=0.35); I^2=8.17%					
Test for overall effect: Z=1.33(P=0.18)					
1.7.4 Heparinoid (subcutaneous) versus control					
Turpie 1987	1/50	0/25		0.41%	4.48[0.07,286.49]
Subtotal (95% CI)	**50**	**25**		**0.41%**	**4.48[0.07,286.49]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					
1.7.5 Heparinoid (intravenous) versus control					
TOAST 1998	10/646	3/635		6.01%	2.91[0.98,8.69]
Subtotal (95% CI)	**646**	**635**		**6.01%**	**2.91[0.98,8.69]**
Total events: 10 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.92(P=0.05)					
1.7.6 Oral vitamin K antagonist versus control					
Marshall 1960	3/26	1/25		1.75%	2.78[0.37,21]
Subtotal (95% CI)	**26**	**25**		**1.75%**	**2.78[0.37,21]**
Total events: 3 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.99(P=0.32)					



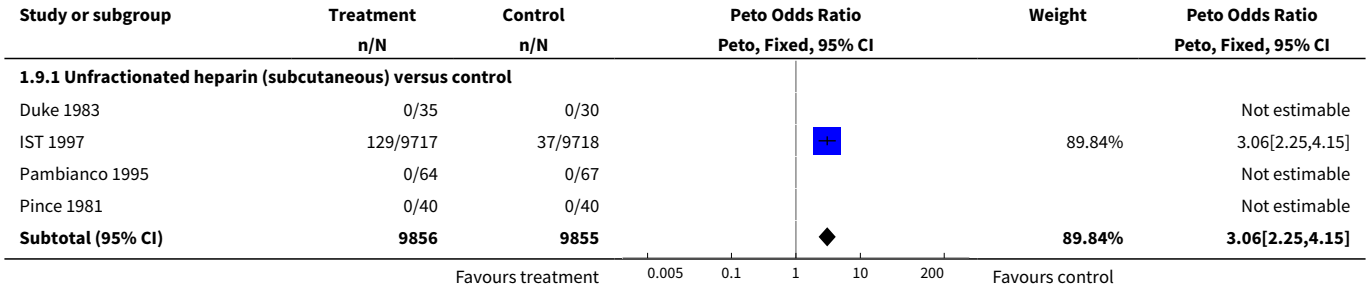


Analysis 1.8. Comparison 1 Anticoagulant versus control in acute presumed ischaemic stroke, Outcome 8 Any recurrent stroke or symptomatic intracranial haemorrhage during treatment period or follow up (> 1 month).

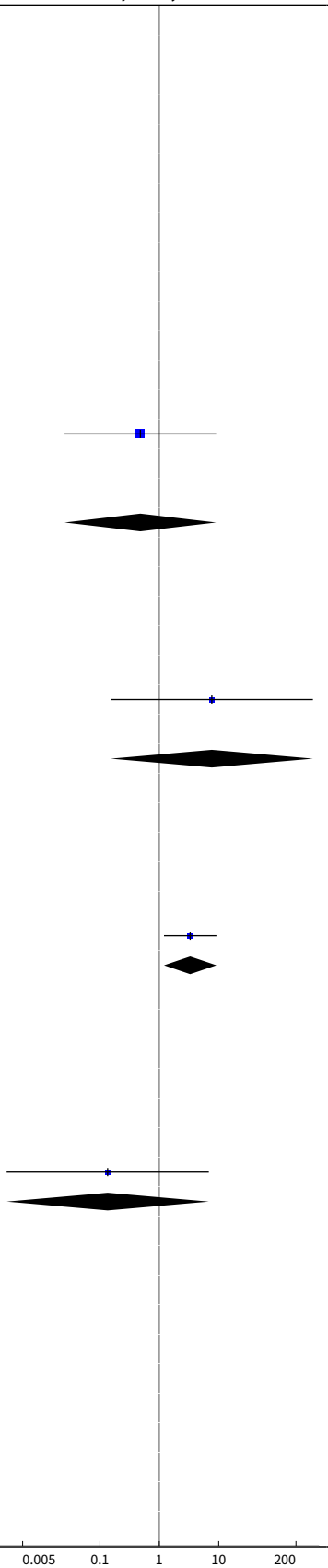


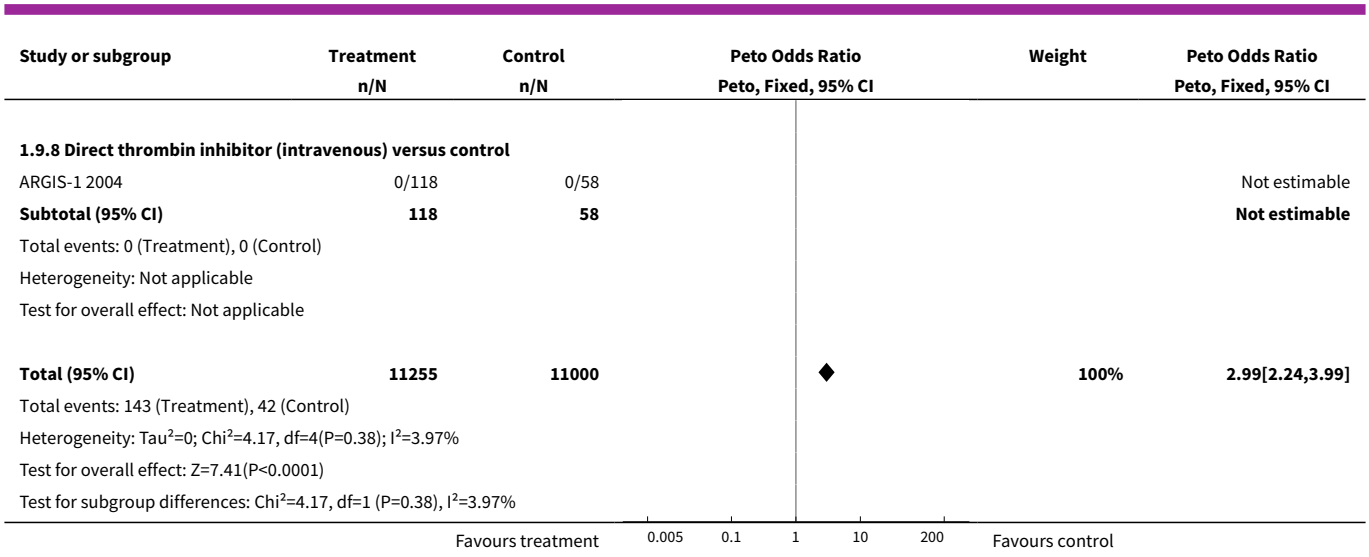


Analysis 1.9. Comparison 1 Anticoagulant versus control in acute presumed ischaemic stroke, Outcome 9 Major extracranial haemorrhage during treatment period.

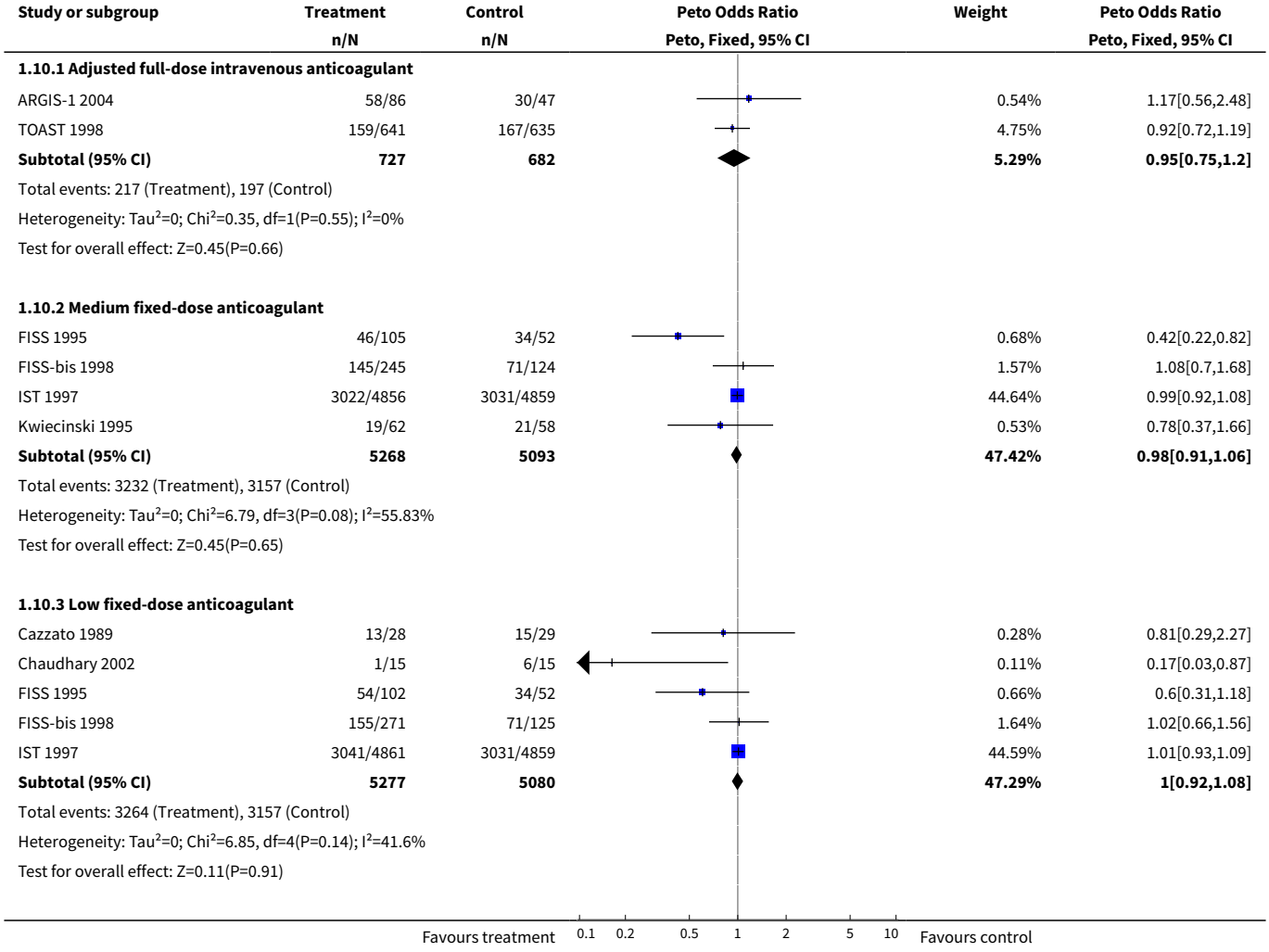


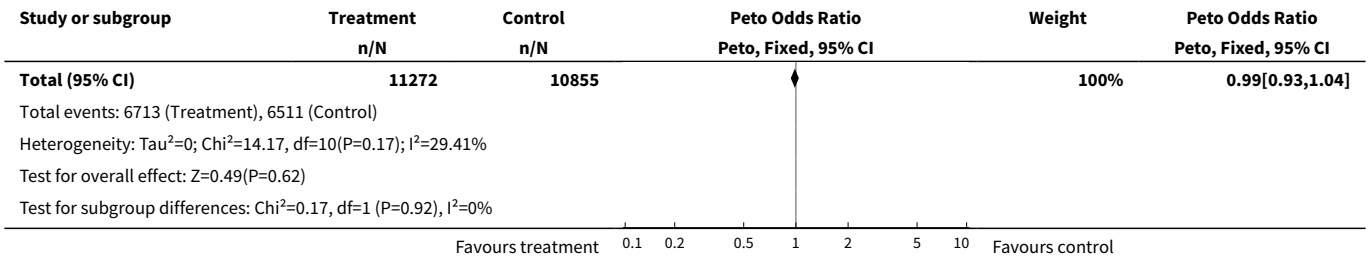
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Total events: 129 (Treatment), 37 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=7.17(P<0.0001)					
1.9.2 Unfractionated heparin (intravenous) versus control					
CESG 1983	0/24	0/21			Not estimable
Subtotal (95% CI)	**24**	**21**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.9.3 Low-molecular-weight heparin versus control					
Chaudhary 2002	0/15	0/15			Not estimable
Elias 1990	0/15	0/15			Not estimable
FISS 1995	1/207	1/105		0.97%	0.48[0.03,9.05]
Prins 1989	0/30	0/30			Not estimable
Sandset 1990	0/52	0/51			Not estimable
Subtotal (95% CI)	**319**	**216**		**0.97%**	**0.48[0.03,9.05]**
Total events: 1 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.49(P=0.62)					
1.9.4 Heparinoid (subcutaneous) versus control					
Cazzato 1989	1/28	0/29		0.55%	7.66[0.15,386.16]
Turpie 1987	0/50	0/25			Not estimable
Subtotal (95% CI)	**78**	**54**		**0.55%**	**7.66[0.15,386.16]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.02(P=0.31)					
1.9.5 Heparinoid (intravenous) versus control					
TOAST 1998	12/646	3/635		8.1%	3.31[1.2,9.15]
Subtotal (95% CI)	**646**	**635**		**8.1%**	**3.31[1.2,9.15]**
Total events: 12 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.3(P=0.02)					
1.9.6 Oral vitamin K antagonist versus control					
Marshall 1960	0/26	0/25			Not estimable
NAT-COOP 1962	0/15	1/15		0.55%	0.14[0,6.82]
Subtotal (95% CI)	**41**	**40**		**0.55%**	**0.14[0,6.82]**
Total events: 0 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1(P=0.32)					
1.9.7 Thrombin inhibitor versus control					
Tazaki 1986	0/104	0/52			Not estimable
Tazaki 1992	0/69	0/69			Not estimable
Subtotal (95% CI)	**173**	**121**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					





Analysis 1.10. Comparison 1 Anticoagulant versus control in acute presumed ischaemic stroke, Outcome 10 Subgroup analysis by anticoagulant dose: effect on death or dependency.





APPENDICES

Appendix 1. Cochrane Library Databases (CENTRAL, CDSR, DARE, HTA)

#1 [mh ^"cerebrovascular disorders"] or [mh ^"basal ganglia cerebrovascular disease"] or [mh ^"brain ischemia"] or [mh "brain infarction"] or [mh ^"hypoxia-ischemia, brain"] or [mh ^"carotid artery diseases"] or [mh ^"carotid artery thrombosis"] or [mh ^"carotid artery, internal, dissection"] or [mh ^"intracranial arterial diseases"] or [mh ^"cerebral arterial diseases"] or [mh ^"infarction, anterior cerebral artery"] or [mh ^"infarction, middle cerebral artery"] or [mh ^"infarction, posterior cerebral artery"] or [mh "intracranial embolism and thrombosis"] or [mh stroke] or [mh ^"vertebral artery dissection"]
#2 isch*mi* near/5 (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva):ti,ab
#3 (brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or mca* or "anterior circulation" or "basilar artery" or "vertebral artery") near/5 (isch*mi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*):ti,ab
#4 #1 or #2 or #3
#5 [mh anticoagulants]
#6 [mh "Blood coagulation factors"/AI,DE] or [mh "Blood coagulation"/AI,DE]
#7 (anticoagul* or antithromb*):ti,ab
#8 [mh ^Warfarin] or [mh ^4-hydroxycoumarins] or [mh ^acenocoumarol] or [mh ^coumarins] or [mh ^dicumarol] or [mh ^"ethyl biscoumacetate"] or [mh ^phenindione] or [mh ^phenprocoumon]
#9 [mh "Vitamin K"/AI]
#10 (warfarin* or coumadin* or coumarin* or cumarin* or phenprocoum* or phenprocum* or dicoumar* or dicumar* or acenocoumar* or acenocumar* or fluindione or phenindione or clorindione or diphenadione or "ethyl biscoumacetate"):ti,ab
#11 (Vitamin next K next antagonist* or VKA or VKAs or "antivitamin K"):ti,ab
#12 [mh antithrombins] or [mh ^"hirudin therapy"] or [mh ^thrombin/AI]
#13 ((direct* near/5 thrombin near/5 inhib*) or DTI or DTIs):ti,ab
#14 (argatroban or MD805 or "MD-805" or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin* or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil):ti,ab
#15 [mh ^"factor Xa"/AI]
#16 (("factor Xa" or "factor 10a" or fXa or "autoprothrombin c" or thrombokinase) near/5 inhib*):ti,ab
#17 (activated near/5 ("factor X" or "factor 10") near/5 inhib*):ti,ab
#18 xabans:ti,ab
#19 (antistasin or apixaban or betrixaban or "du 176b" or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or "ym 150" or ym150 or LY517717 or darexaban or edoxaban or SSR126517E or fidexaban or idrabiotaparinux or letaxaban or tanogitran or taxexaban):ti,ab
#20 [mh ^heparin] or [mh "heparin, low-molecular-weight"] or [mh ^heparinoids]
#21 (heparin* or lmwh* or enoxaparin* or glycosaminoglycan* or nadroparin* or mesoglycan* or tedelparin* or certoparin or tinzaparin or parnaparin or dalteparin or reviparin or fraxiparin* or danaparoid or lomoparan or "org 10172" or mesoglycan or pentosan next polysul* or sp54 or "sp-54" or cy222 or "cy-222" or cy216 or "cy-216" or dermatan next sul* or heparan next sul*):ti,ab
#22 {or #5-#21}
#23 #4 and #22
#24 atrial fibrillation:ti
#25 #23 not #24

Appendix 2. MEDLINE (Ovid)

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or brain ischemia/ or exp brain infarction/ or hypoxia-ischemia, brain/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid artery, internal, dissection/ or intracranial arterial diseases/

or cerebral arterial diseases/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or exp "intracranial embolism and thrombosis"/ or exp stroke/ or vertebral artery dissection/
2. (isch?emi$ adj5 (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 or basilar artery or vertebral artery) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. 1 or 2 or 3
5. exp anticoagulants/
6. exp Blood coagulation factors/ai, de or exp Blood coagulation/ai, de
7. (anticoagul$ or antithromb$).tw.
8. Warfarin/ or 4-hydroxycoumarins/ or acenocoumarol/ or coumarins/ or dicumarol/ or ethyl biscoumacetate/ or phenindione/ or phenprocoumon/
9. exp Vitamin K/ai
10. (warfarin$ or coumadin$ or coumarin$ or cumarin$ or phenprocoum$ or phenprocum$ or dicoumar$ or dicumar$ or acenocoumar$ or acenocumar$ or fluindione or phenindione or clorindione or diphenadione or ethyl biscoumacetate).tw,nm.
11. (Vitamin K antagonist$ or VKA or VKAs or antivitamin K).tw.
12. exp antithrombins/ or hirudin therapy/ or thrombin/ai
13. ((direct$ adj5 thrombin adj5 inhib$) or DTI$1).tw.
14. (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin$ or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil).tw,nm.
15. factor Xa/ai
16. ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj5 inhib$).tw.
17. (activated adj5 (factor X or factor 10) adj5 inhib$).tw.
18. xabans.tw.
19. (antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717 or darexaban or edoxaban or SSR126517E or fidexaban or idrabiotaparinux or letaxaban or tanogitran or taxexaban).tw,nm.
20. heparin/ or exp heparin, low-molecular-weight/ or heparinoids/
21. (heparin$ or lmwh$ or enoxaparin$ or glycosaminoglycan$ or nadroparin$ or mesoglycan$ or tedelparin$ or certoparin or tinzaparin or parnaparin or dalteparin or reviparin or fraxiparin$ or danaparoid or lomoparan or org 10172 or mesoglycan or pentosan polysul$ or sp54 or sp-54 or cy222 or cy-222 or cy216 or cy-216 or dermatan sul$ or heparan sul$).tw,nm.
22. or/5-21
23. Randomized Controlled Trials as Topic/
24. random allocation/
25. Controlled Clinical Trials as Topic/
26. control groups/
27. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
28. double-blind method/
29. single-blind method/
30. Placebos/
31. placebo effect/
32. Research Design/
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
36. (random$ or RCT or RCTs).tw.
37. (controlled adj5 (trial$ or stud$)).tw.
38. (clinical$ adj5 trial$).tw.
39. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
40. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
41. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
42. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
43. (placebo$ or sham).tw.
44. trial.ti.
45. (assign$ or allocat$).tw.
46. controls.tw.
47. or/23-46
48. 4 and 22 and 47
49. exp animals/ not humans.sh.
50. 48 not 49
51. atrial fibrillation.ti.

52. 50 not 51

Appendix 3. EMBASE (Ovid)

1. brain infarction/ or brain stem infarction/ or cerebellum infarction/ or exp brain ischemia/ or carotid artery disease/ or exp carotid artery obstruction/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp occlusive cerebrovascular disease/ or stroke patient/
2. (isch?emi$ adj5 (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 or basilar artery or vertebral artery) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus $ or hypoxi$)).tw.
4. 1 or 2 or 3
5. exp anticoagulant agent/
6. anticoagul$.tw.
7. antithromb$.tw.
8. coumarin derivative/ or 4 hydroxycoumarin/ or 4 hydroxycoumarin derivative/ or acenocoumarol/ or coumarin/ or dicoumarol/ or ethyl biscoumacetate/ or phenprocoumon/ or warfarin/ or phenindione/
9. antivitamin k/
10. (warfarin$ or coumadin$ or coumarin$ or cumarin$ or phenprocoum$ or phenprocum$ or dicoumar$ or dicumar$ or acenocoumar$ or acenocumar$ or fluindione or phenindione or clorindione or diphenadione or ethyl biscoumacetate).tw.
11. (Vitamin K antagonist$ or VKA or VKAs or antivitamin K).tw.
12. exp thrombin inhibitor/
13. ((direct$ adj5 thrombin adj5 inhib$) or DTI$1).tw.
14. (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin$ or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil).tw.
15. blood clotting factor 10a inhibitor/
16. ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj5 inhib$).tw.
17. (activated adj5 (factor X or factor 10) adj5 inhib$).tw.
18. xabans.tw.
19. (antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717 or darexaban or edoxaban or SSR126517E or fidexaban or idrabiotaparinux or letaxaban or tanogitran or taxexaban).tw.
20. heparin derivative/ or heparin/ or heparinoid/ or exp low molecular weight heparin/
21. (heparin$ or lmwh$ or enoxaparin$ or glycosaminoglycan$ or nadroparin$ or mesoglycan$ or tedelparin$ or certoparin or tinzaparin or parnaparin or dalteparin or reviparin or fraxiparin$ or danaparoid or lomoparan or org 10172 or mesoglycan or pentosan polysul$ or sp54 or sp-54 or cy222 or cy-222 or cy216 or cy-216 or dermatan sul$ or heparan sul$).tw.
22. or/5-21
23. Randomized Controlled Trial/
24. Randomization/
25. Controlled Study/
26. control group/
27. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/
28. Double Blind Procedure/
29. Single Blind Procedure/ or triple blind procedure/
30. placebo/
31. (random$ or RCT or RCTs).tw.
32. (controlled adj5 (trial$ or stud$)).tw.
33. (clinical$ adj5 trial$).tw.
34. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
35. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
36. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
37. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
38. placebo$.tw.
39. trial.ti.
40. (assign$ or allocat$).tw.
41. controls.tw.
42. or/23-41
43. 4 and 22 and 42
44. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
45. 43 not 44
46. (atrial fibrillation or myocardial or coronary or cardiac or heart or renal or subarachnoid or arteritis or hypertens$ or aortic or cancer or pregnan$ or dementia or diabetes or sickle cell or aneurysm$ or cardiopulmonary or migrain$).ti.

47. 45 not 46

Appendix 4. Ongoing trials registries search

ClinicalTrials.gov
"stroke" AND "anticoagulants"
"stroke" AND "heparin"

Internet Stroke Center Stroke Trials Registry
"stroke" AND "anticoagulants"
"stroke" AND "heparin"

ISRCTN Registry
"stroke" AND "anticoagulants"
"stroke" AND "heparin"

FEEDBACK

Conclusions too weak, 25 June 2007

Summary

This review of anticoagulant trials, including over 22,000 patients with acute ischemic stroke, found no net benefit with the use of any anticoagulant. Consequently, the implications for practice and implications for research are too timid. The implication for practice should say that anticoagulants should be contraindicated in patients with acute ischemic stroke. The implications for research should say that further trials of anticoagulants in acute ischemic stroke would be unethical.

Reply

This comment was submitted before the 2008 update was performed. The wording of the Authors' conclusions section has been modified to be more in keeping with this comment.
Note: the response to this feedback was delayed by a number of unavoidable administrative factors.

Contributors

Commenter: David A Cundiff MD
Reply: Peter Sandercock

WHAT'S NEW

Date	Event	Description
18 September 2014	New search has been performed	We have searched the literature for new relevant studies to June 2014. We identified one small new ongoing study, but did not identify any new studies for inclusion. We have reformatted and updated the text throughout
18 September 2014	New citation required but conclusions have not changed	The conclusions are unchanged

HISTORY

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

Date	Event	Description
9 January 2009	Feedback has been incorporated	Feedback on the previous version of this review had not been incorporated. This omission has now been rectified in this small revision to the 2008 update.
7 November 2008	Amended	Duplicate text in 'Updated' event of 11 January 2008 has been deleted.
17 March 2008	Amended	Converted to new review format.
11 January 2008	New citation required but conclusions have not changed	New co-author: Ayeesha Kamal has replaced Gordon Gubitz.
11 January 2008	New search has been performed	The searches have been updated to October 2007. Two trials (ARGIS-1 2004; Chaudhary 2002), with 201 participants, were included in this update, bringing the total number of trials to 24 involving 23,547 participants. The text has been extensively revised and updated.

CONTRIBUTIONS OF AUTHORS

Peter Sandercock designed the original 1993 review of anticoagulant versus control, double-checked the data and supervised the analysis and writing of this report. Edward Kane did the new literature searches and helped reformat and rewrite this update.
Ayeesha Kamal did the new literature searches, extracted the new data , performed the analysis and helped rewrite the text of the 2008 update.
Carl Counsell prepared the first version of the review and helped with the analysis and text of subsequent updates.

DECLARATIONS OF INTEREST

Dr Sandercock was the principal investigator of the International Stroke Trial and Dr Counsell was also on the Steering Committee of this trial (IST 1997). Edward Kane has no conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- University of Edinburgh, UK.

External sources

- Wellcome Trust, UK.
- Medical Research Council, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [adverse effects] [*therapeutic use]; Brain Ischemia [*drug therapy] [prevention & control]; Randomized Controlled Trials as Topic; Risk; Stroke [*drug therapy] [prevention & control]

MeSH check words

Humans