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Anticoagulants for acute ischaemic stroke (Review)

Wang X, Ouyang M, Yang J, Song L, Yang M, Anderson CS

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[Intervention Review]

Anticoagulants for acute ischaemic stroke

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ABSTRACT

Background

Stroke is the third leading cause of early death worldwide. Most ischaemic strokes are caused by a blood clot blocking an artery in the brain. Patient outcomes might be improved if they are offered anticoagulants that reduce their risk of developing new blood clots and do not increase the risk of bleeding. This is an update of a Cochrane Review first published in 1995, with updates in 2004, 2008, and 2015.

Objectives

To assess the effectiveness and safety of early anticoagulation (within the first 14 days of onset) for 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:

• reduced risk of death or dependence in activities of daily living a few months after stroke onset;

• reduced risk of early recurrent ischaemic stroke;

• increased risk of symptomatic intracranial and extracranial haemorrhage; and

• reduced risk of deep vein thrombosis and pulmonary embolism.

Search methods

We searched the Cochrane Stroke Group Trials Register (August 2021); the Cochrane Database of Systematic Reviews (CDSR); the Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 7), in the Cochrane Library (searched 5 August 2021); MEDLINE (2014 to 5 August 2021); and Embase (2014 to 5 August 2021). 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 data. We assessed the overall certainty of the evidence for each outcome using RoB1 and GRADE methods.

Main results

We included 28 trials involving 24,025 participants. Quality of the trials varied considerably. We considered some studies to be at unclear or high risk of selection, performance, detection, attrition, or reporting bias. Anticoagulants tested were standard unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors. Over 90% of the evidence is related to effects of anticoagulant therapy initiated within the first 48 hours of onset. No evidence suggests that early anticoagulation reduced the odds of death or dependence at the end of follow-up (odds ratio (OR) 0.98, 95% confidence interval (CI) 0.92 to 1.03; 12 RCTs, 22,428 participants; high-certainty evidence). Similarly, we found no evidence suggesting that anticoagulant therapy started within the first 14 days of stroke onset reduced the odds of death from all causes (OR 0.99, 95% CI 0.90 to 1.09; 22 RCTs, 22,602 participants; low-certainty evidence) during the treatment period. Although early anticoagulant therapy was associated with fewer recurrent ischaemic strokes (OR 0.75, 95% CI 0.65 to 0.88; 12 RCTs, 21,665 participants; moderate-certainty evidence), it was also associated with an increase in symptomatic intracranial haemorrhage (OR 2.47; 95% CI 1.90 to 3.21; 20 RCTs, 23,221 participants; moderate-certainty evidence). Similarly, early anticoagulation reduced the frequency of symptomatic pulmonary emboli (OR 0.60, 95% CI 0.44 to 0.81; 14 RCTs, 22,544 participants; high-certainty evidence), but this benefit was offset by an increase in extracranial haemorrhage (OR 2.99, 95% CI 2.24 to 3.99; 18 RCTs, 22,255 participants; moderate-certainty evidence).

Authors' conclusions

Since the last version of this review, four new relevant studies have been published, and conclusions remain consistent. People who have early anticoagulant therapy after acute ischaemic stroke do not demonstrate any net short- or long-term benefit. Treatment with anticoagulants reduced recurrent stroke, deep vein thrombosis, and pulmonary embolism but increased bleeding risk. Data do not support the routine use of any of the currently available anticoagulants for acute ischaemic stroke.

PLAIN LANGUAGE SUMMARY

Early treatment with blood-thinning drugs for people who have had a stroke

Review question
We wanted to know whether people treated with anticoagulants (blood-thinning drugs) soon after having a stroke got better or not, and whether they had problems with bleeding.

Background
Millions of people around the world have a stroke every year. Most strokes take place when a blood clot blocks a blood vessel leading to the brain. When the blood supply to the brain is restricted or blocked, brain cells begin to die. This can lead to brain injury, which can be permanent, causing disability and possibly death. Damage from a stroke can cause arm or leg weakness, or difficulties with language or vision. Strokes are sometimes fatal but more often leave survivors unable to do the things they used to do. Because strokes are common and cause such damage, researchers are looking at ways to get rid of the blood clot soon after the stroke happens. One way to do this is to use blood-thinning drugs called anticoagulants. If patients respond well to anticoagulants, they might be able to avoid the bad effects of a stroke. The main problem with anticoagulants is that if they cause bleeding, the patient can have very serious outcomes from this.

Search date
The evidence is current to August 2021.

Study characteristics
To find the best answer, we looked for studies in which investigators compared any anticoagulant to another medicine, to a dummy medicine that does not contain any active ingredients (placebo), or to normal care. To make the comparison fair, all patients in these studies must have had the same random chance (like the flip of a coin) to receive the anticoagulant, the other treatment, or normal care. We included in this updated review 28 studies involving 24,025 people with stroke. Two studies enrolled participants within 12 hours of stroke onset, four within 24 hours, and 10 within 48 hours.

Key results
People treated with anticoagulants did not have less long-term disability, and they experienced more bleeding. Anticoagulant-treated patients had a lesser chance of developing blood clots in their legs and in their lungs following their stroke, but these benefits were offset by an increased number of bleeds.

Certainty of the evidence
We used standard methods to assess the certainty of the evidence. We rated our confidence in the evidence based on factors such as study methods, numbers of participants included in the studies, and consistency of findings across studies. Low-certainty evidence means we are uncertain about the results. In the same way, high-certainty evidence means we are very certain about the results of this review.

Conclusion

This review did not provide any evidence to suggest that early use of anticoagulants is beneficial overall for people with stroke caused by blood clots. More research is needed to find out if there are ways to select people with stroke who will benefit most from anticoagulants without suffering the bleeding complications.

Summary of findings 1. Summary of findings table - Anticoagulant compared to control in acute presumed ischaemic stroke

Anticoagulant compared to control in acute presumed ischaemic stroke

Patient or population: acute presumed ischaemic stroke
Setting: hospital
Intervention: anticoagulant
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with anticoagulant				
Dead or dependent at end of follow-up (if > 1 month)	598 per 1000	**593 per 1000** (578 to 605)	**OR 0.98** (0.92 to 1.03)	22428 (13 RCTs)	⊕⊕⊕⊕ High	-
Death from all causes during treatment period	86 per 1000	**85 per 1000** (78 to 93)	**OR 0.99** (0.90 to 1.09)	22602 (22 RCTs)	⊕⊕⊖⊖ Low	Only 3 studies included in this analysis had low risk in each domain; only 2 out of 22 studies enrolled more than 500 patients, clearly underpowered
Deep vein thrombosis during treatment period	443 per 1000	**143 per 1000** (107 to 188)	**OR 0.21** (0.15 to 0.29)	916 (10 RCTs)	⊕⊖⊖⊖ Very low	No studies included in this analysis had low risk in each domain; all the studies were too underpowered to draw a firm conclusion; publication bias has been detected
Recurrent ischaemic or unknown stroke during treatment period	36 per 1000	**27 per 1000** (24 to 32)	**OR 0.75** (0.65 to 0.88)	21665 (12 RCTs)	⊕⊕⊕⊖ Moderate	Only 2 studies included in this analysis had low risk in each domain
Symptomatic intracranial haemorrhage during treatment period	5 per 1000	**12 per 1000** (9 to 16)	**OR 2.47** (1.90 to 3.21)	23221 (21 RCTs)	⊕⊕⊕⊖ Moderate	Publication bias has been detected
Symptomatic pulmonary embolism during treatment period	9 per 1000	**6 per 1000** (4 to 8)	**OR 0.60** (0.44 to 0.81)	22544 (14 RCTs)	⊕⊕⊕⊕ High	-

Major extracranial haemorrhage during treatment period	4 per 1000	**11 per 1000** (9 to 15)	**OR 2.99** (2.24 to 3.99)	22255 (18 RCTs)	⊕⊕⊕⊖ Moderate	Publication bias has been detected

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423948318800395805.

BACKGROUND

Description of the condition

Stroke was the third leading cause of disability-adjusted life-years and early death among people of all ages worldwide in 2017 (Kyu-2018). Due to demographic (aging population) and lifestyle changes, the global burden of stroke is increasing, with the greatest burden noted in low- and middle-income countries (Feigin 2014). In Western societies, ischaemic stroke is the most frequent pathological subtype of stroke (~80%) and is usually caused by a blood clot blocking flow in an artery supplying parts of the brain (Feigin 2009).

Description of the intervention

Anticoagulants are agents that act on the coagulation cascade to reduce fibrin polymerisation and thrombus formation; they 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 - placebo or no treatment - delivered along with standard interventions of the respective healthcare systems.

Heparins are administered parenterally (intravenously or subcutaneously) and so have 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 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 that act primarily to inhibit factor Xa. They have a longer half-life, greater bioavailability, 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, by reducing the propagation of a thrombus in an intracerebral artery, may decrease the volume of infarcted cerebral tissue and so decrease the neurological deficit and risks 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 may increase the 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 2020. We included all randomised trials of anticoagulants versus control for 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) for 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:

- reduced risk of death or dependence in activities of daily living a few months after stroke onset;
- reduced risk of early recurrent ischaemic stroke;
- increased risk of symptomatic intracranial and extracranial haemorrhage; and
- 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 for 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) also are not included in this review. We did not include trials in which allocation to treatment or control group was not truly random, or in which allocation was not adequately concealed (e.g. allocation by alternation, date of birth, hospital number, day of the week, open random number list), because foreknowledge of treatment allocation could lead to biased treatment allocation, leading to overestimation of the treatment effect by up to 30% (Odgaard-Jensen 2011). We included trials in which it is unclear whether the method of randomisation provided adequate concealment of allocation.

Types of participants

This review was confined to early treatment of acute ischaemic stroke; therefore we excluded the following types of trials: those that randomised participants more than 14 days after stroke onset, those that included only people with TIAs, and those that included only 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 a majority of such strokes are ischaemic (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). Use of thrombolytic agents for acute ischaemic stroke is the topic of a separate Cochrane Review (Wardlaw 2014), as is 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. For both groups, we sought outcome information regarding the numbers of participants who met the following outcomes.

Primary outcomes

- Death or dependency (i.e. people who were dead or were dependent on help from other people for their activities of daily living), at least one month after 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

- Participants who died from any cause during the scheduled treatment period (generally shorter than the scheduled follow-up period)
- Participants who died from any cause during the scheduled follow-up period (greater than one month after stroke)
- 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 during the scheduled treatment period and during scheduled follow-up. These methods detected clinically silent deep vein thrombosis while confirming or refuting the diagnosis for 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
- Particpants with recurrent stroke during the treatment period and during follow-up that was either definitively ischaemic (haemorrhage excluded by brain imaging or autopsy) or of unknown type (no brain imaging or autopsy performed)
- Participants with symptomatic intracranial (intracerebral or extracerebral) haemorrhage, including symptomatic haemorrhagic transformation of the cerebral infarct, during the scheduled treatment period and during follow-up. Haemorrhage must have been confirmed by appropriate brain imaging after clinical deterioration, or by autopsy
- Participants with any recurrent stroke or symptomatic intracranial haemorrhage during the treatment period or during long-term follow up (as previously defined)
- 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
- 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, major haemorrhage 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 reported only data on our secondary outcomes.

Search methods for identification of studies

See the 'Specialized register' section at the Cochrane Stroke Group website. We searched for trials published 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 April 2020) and the following bibliographic databases and trials registers.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 7), in the Cochrane Library (Appendix 1).
- Cochrane Database of Systematic Reviews (CDSR; 2021, Issue 7), in the Cochrane Library (Appendix 1).
- Database of Reviews of Effects (DARE; 2014, Issue 6), in the Cochrane Library (Appendix 1).
- Health Technology Assessment Database (HTA; 2014, Issue 6), in the Cochrane Library (Appendix 1).
- MEDLINE (Ovid; 2014 to August 2021) (Appendix 2).
- Embase (Ovid; 2014 to 14 August 2021) (Appendix 3).

Using a comprehensive search strategy, the Cochrane Stroke Group Trials Search Co-ordinator had already completed a retrospective search of MEDLINE and Embase for all stroke trials to January 2014 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 2014 onwards.

Searching other resources

- ClinicalTrials.gov (https://clinicaltrials.gov; searched 5 August 2021) (Appendix 4)
- International Standard Randomized Controlled Trials Number (ISRCTN) Registry (http://www.isrctn.com/; searched 5 August 2021) (Appendix 4)
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 5 August 2021) (Appendix 4)
- We scanned the reference lists of all relevant papers
- For previous versions of this review:
  - 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), and Sanofi Winthrop (nadroparin and CY 222);
  - 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 included in the Cochrane Stroke Group Trials Register; and
  - in August 1998, we searched the trials register held by the Antithrombotic Trialists' (ATT) Collaboration, but this is no longer available and relevant trials from the register are now contained in the Cochrane Stroke Group Trials Register

Data collection and analysis

We followed standard Cochrane methodological procedures. For this update, Joshua Cheyne (Cochrane Stroke Group Information Specialist) performed the searches. XW and MO then independently screened all titles and abstracts of identified references and excluded obviously irrelevant studies. XW obtained full-text articles of the remaining studies, and both XW and MO independently assessed these for inclusion or exclusion. We resolved any disagreements by discussion with LS, JY, and CA.

Selection of studies

Two review authors (PS and CC, for trials included in the first version of this review; PS and Gordon Gubitz for the proceeding two updates following the original review; Ayeesha Kamal and PS for the 2008 update; PS and EK for the 2015 update; XW and MO for this version) 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 participants were subsequently deemed ineligible or were otherwise excluded from treatment or follow-up, to allow an intention-to-treat (ITT) analysis. We also sought data on use of brain imaging prior to randomisation, delay from stroke onset to trial entry, types of patients included, and types of anticoagulant regimens used. If any of the above data were not available in the publications, we sought further information by corresponding with the trialists.

Assessment of risk of bias in included studies

We assessed the risk of bias of each of the included trials using the following criteria of internal validity: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, adequate reporting and handling of missing outcome data, selective outcome reporting, and other risks of bias. We followed the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors (MO, XW) independently assessed risk of bias for the included studies using RoB1. We followed GRADE recommendations to determine the certainty of the evidence (Guyatt 2008). This involved considering risk of bias together with inconsistency, indirectness, imprecision, and publication bias. Two review authors (MO, XW) completed this assessment.

Measures of treatment effect

Results reported in the text are odds ratios (ORs; i.e. ratios 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) by using a standard method (Altman 1996). When relevant, we expressed the absolute effects of treatment on each outcome 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 was calculated as the number needed to treat to harm (NNTH). To calculate NNTBs or NNTHs, we used the NNT calculator at https://www2.ccrb.cuhk.edu.hk/stat/confidence%20interval/CI%20for%20ratio.htm. This applies the point estimate of relative effect and its 95% confidence interval (CI), then calculates NNTB or NNTH for a specified control event rate.

Unit of analysis issues

All included studies were trials in which individuals were randomised and follow-up was generally provided to a prespecified and fixed time point; all analyses were by ITT where possible (see Dealing with missing data). For outcomes for which 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. For 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 identified and measured statistical and clinical heterogeneity as recommended in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021). We estimated heterogeneity between trial results using the I^2 statistic (Deeks 2021). We defined thresholds for interpreting heterogeneity (I^2) as follows.

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

Evaluation of heterogeneity was not based on I^2 alone, as the importance of consistency depends on several factors, but rather included an overall evaluation of the data. We also considered the P value, noting that with $P < 0.05$, there was likely to be heterogeneity.

Assessment of reporting biases

We attempted to minimise publication bias by using a comprehensive search strategy that included searching for unpublished studies and searching trials registers. We examined the funnel plot for any evidence of asymmetry for three outcomes. Analyses including the greatest numbers of trials (and hence with the greatest statistical power) examined effects of treatment on death during the treatment period, death from all causes at final follow-up, and deep vein thrombosis.

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 agents. 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.

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

Subgroup analysis and investigation of heterogeneity

For this update, we performed subgroup analyses for the primary outcome by:

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

Sensitivity analysis

For this update, we performed the following sensitivity analyses for the primary outcome, 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 relevant to the review.

In the previous version of this review, we performed numerous sensitivity analyses to investigate whether 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, or 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. For future updates of the review, we do not plan to repeat these analyses unless substantial new trial data have been added.

Summary of findings and assessment of the certainty of the evidence

We used 'Summary of findings' tables to summarise the data comparing control and anticoagulation on (1) death or dependency at the end of follow-up (if > 1 month), (2) death from all causes during the treatment period, (3) deep vein thrombosis during the treatment period, (4) recurrent ischaemic or unknown stroke during the treatment period, (5) symptomatic intracranial haemorrhage during the treatment period, (6) symptomatic pulmonary embolism during the treatment period, and (7) major extracranial haemorrhage during the treatment period. We used GRADE methods to assess the overall certainty of evidence for each outcome (Guyatt 2008).

RESULTS

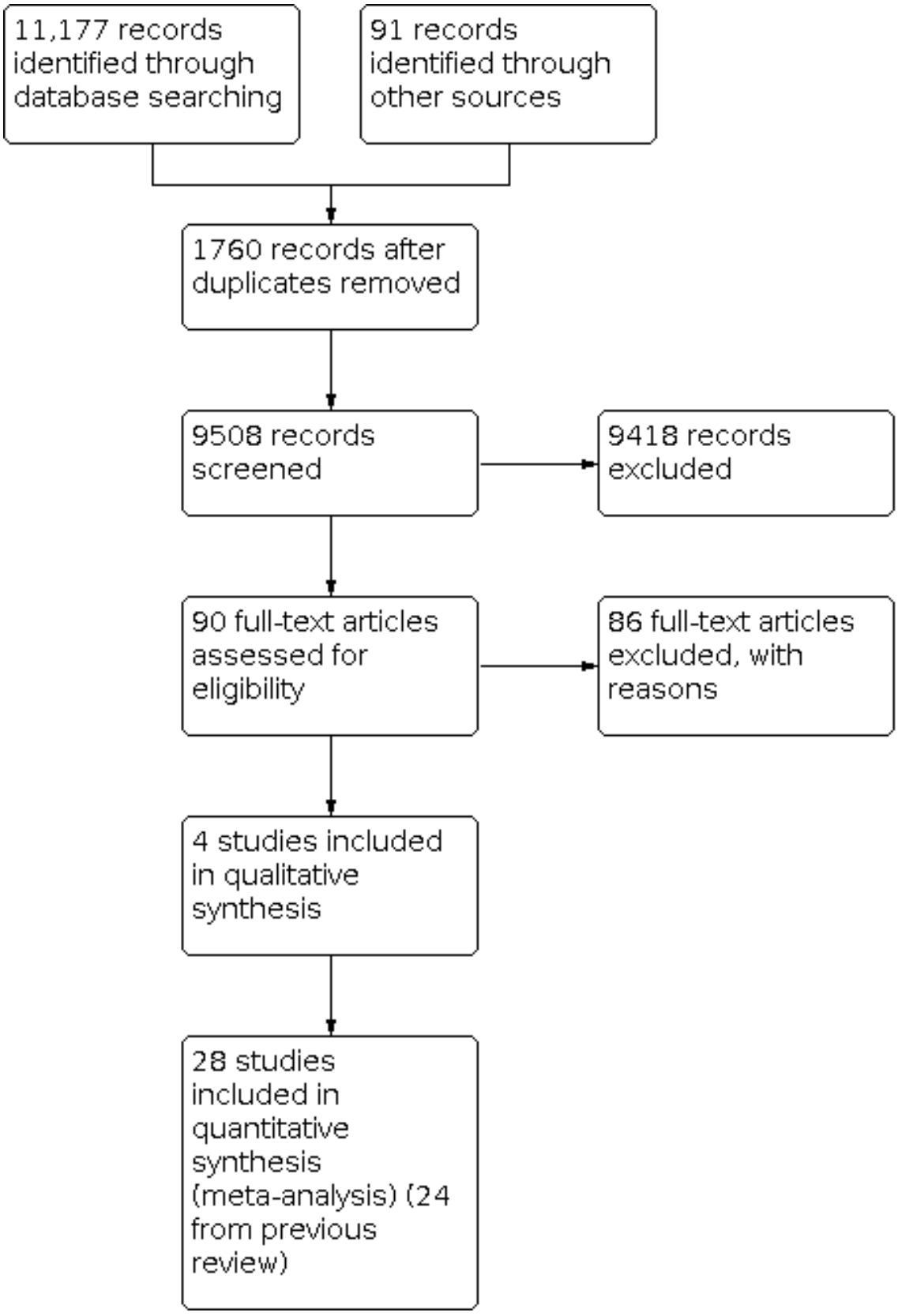
Description of studies

See Characteristics of ongoing studies and Characteristics of excluded 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 we removed duplicate records, we screened the titles and abstracts of 9508 records from these electronic bibliographic databases and obtained the full text of 90 studies, of which we excluded 86 studies, leaving four new trials for inclusion. The total number of included studies in this review is 28. See Figure 1.

Figure 1. Study flow diagram for 2020 update.



We identified six new ongoing trials from searches of trials registers (see Characteristics of ongoing studies).

Included studies

We included in this review 28 trials with a total of 24,025 participants. Summary details for these trials are given in the Characteristics of included studies table. Of the 28 included studies, two enrolled participants within 12 hours of stroke onset (ARGIS-1 2004; ARTSS-2 2017), four enrolled participants within 24 hours of stroke onset (Dluha 2016; FISS-bis 1998; Sarma 2003; TOAST 1998), 11 enrolled participants within 48 hours of stroke onset (Cazzato 1989; CESG 1983; Duke 1983; Duke 1986; Elias 1990; FISS 1995; IST 1997; Kwiecinski 1995; Liu 2020; 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 men than women and excluded people thought to be at high risk of bleeding (e.g. clotting disorders, hepatic failure, renal failure). In addition, 13 trials excluded people with a significant degree of hypertension (generally diastolic pressure > 120 mmHg or systolic pressure > 180 mmHg), and 10 trials excluded comatose people.

The scheduled period of anticoagulant treatment in included trials was one to two weeks in 24 trials, and one month in four trials. The anticoagulants used were (one trial used two types of anticoagulants (Dluha 2016) and therefore was considered as two trials):

- standard unfractionated subcutaneous heparin (six trials);
- standard unfractionated intravenous heparin (three trials);
- low-molecular-weight heparins (10 trials: two dalteparin, four 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 (five trials: two MD805 trials, three argatroban).

In trials using oral vitamin K antagonists, heparin was given intravenously for the first few days to provide rapid anticoagulation (Marshall 1960; NAT-COOP 1962). Five trials randomised between two doses of anticoagulant as well as control (ARTSS-2 2017; Dluha 2016; FISS 1995; FISS-bis 1998; IST 1997); for the main analyses in this review, we combined the two anticoagulant groups for these trials.

Eighteen trials routinely performed a CT head scan for all patients to rule out haemorrhage before randomisation (ARGIS-1 2004; ARTSS-2 2017; Cazzato 1989; CESG 1983; Dluha 2016; Duke 1986; Elias 1990; FISS 1995; FISS-bis 1998; Kwiecinski 1995; Pambianco 1995; Prins 1989; Sarma 2003; Sandset 1990; Tazaki 1986; Tazaki 1992; TOAST 1998; Turpie 1987). Three trials performed CT for most patients (Duke 1983; IST 1997; Vissinger 1995): 81% 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 risks of anticoagulation are greater in those with intracerebral haemorrhage, although such 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 effects of heparin in this subgroup was reported in a paper published in 2001 (Saxena 2001).

The duration of follow-up in included 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 participants beyond 14 days (Elias 1990; McCarthy 1977; Pince 1981; Prins 1989), and only 14 trials followed participants longer than one month (ARGIS-1 2004; ARTSS-2 2017; Chaudhary 2002; Dluha 2016; Duke 1986; FISS 1995; FISS-bis 1998; IST 1997; Kwiecinski 1995; Liu 2020; 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 (i.e. between three and 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. Eleven 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; ARTSS-2 2017; Cazzato 1989; Chaudhary 2002; Dluha 2016; FISS 1995; FISS-bis 1998; IST 1997; Kwiecinski 1995; Liu 2020; TOAST 1998). Other important outcomes, including recurrent stroke or intracranial haemorrhage, were assessed but, once again, only by the more recent trials, which included large numbers of participants. Quality of life assessments were undertaken only in ARTSS-2 2017.

Excluded studies

We excluded 103 studies for a variety of reasons (see Characteristics of excluded studies).

Risk of bias in included studies

Two review authors independently assessed risk of bias in all included studies across the following domains: random sequence generation and allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data

(attrition bias); selective reporting (reporting bias); and other potential sources of bias.

See 'Risk of bias' tables in Characteristics of included studies, in the overall 'Risk of bias' graph (Figure 2), and in the risk of bias summary (Figure 3).

Figure 2.

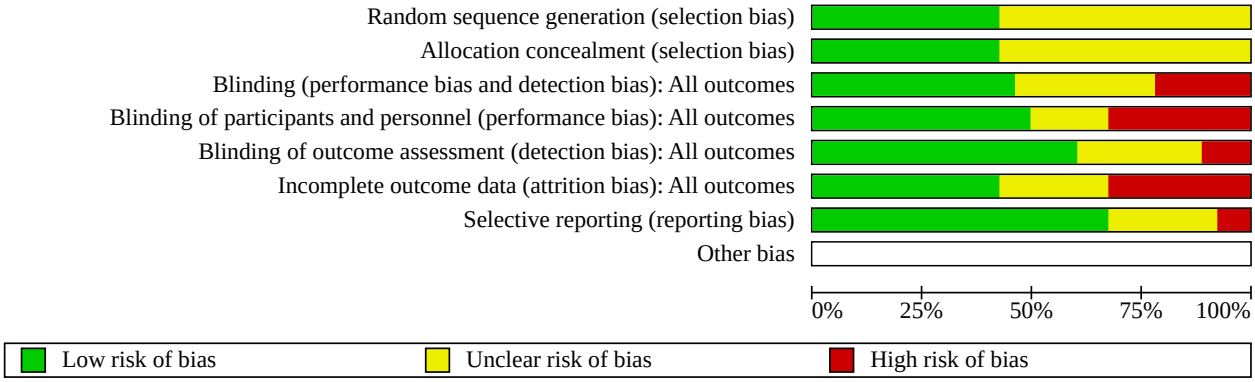


Figure 3.

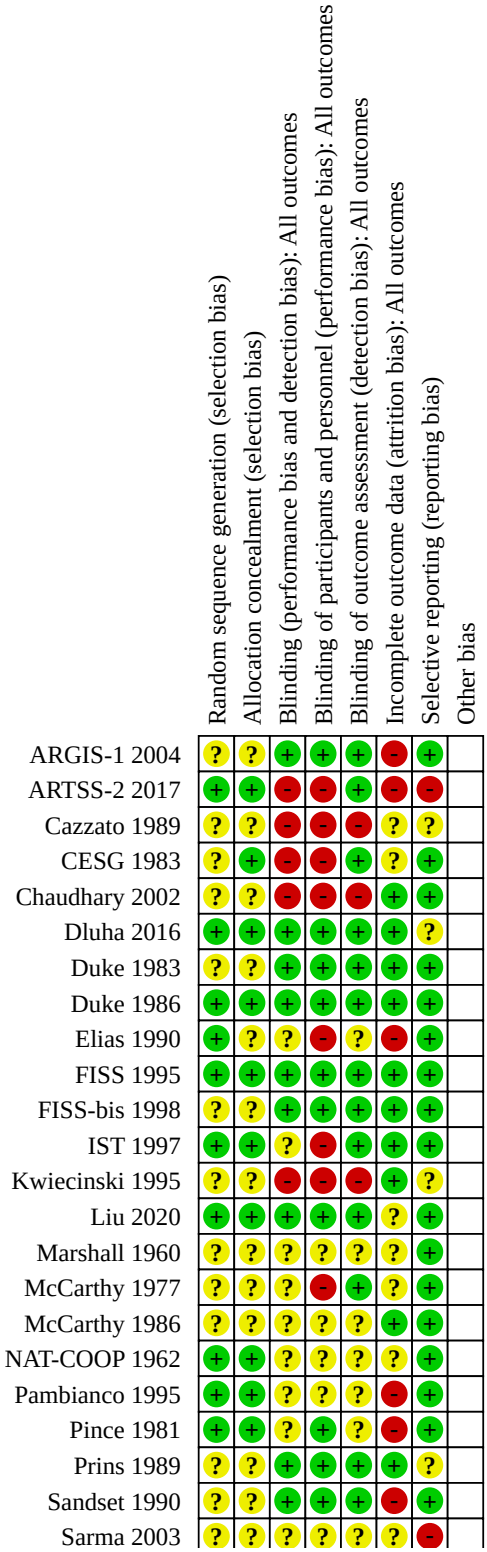
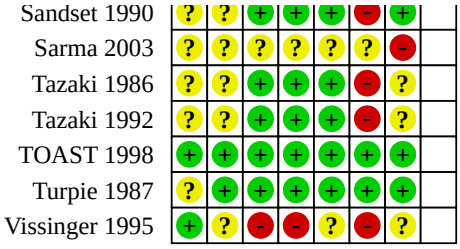


Figure 3. (Continued)



Randomisation

There was marked variation in the quality of included trials. In 12 trials, the method of randomisation adequately prevented foreknowledge of treatment allocation; therefore they were at low risk. The remaining 16 trials had unclear risk. 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 10 trials. Six trials stated that sealed envelopes were used, but in five of these, it is 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

Twelve trials had low risk of bias, and the remaining 16 trials had unclear risk. 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, Pince 1981, and Sarma 2003.

Blinding

Thirteen trials had low risk, six trials had high risk, and the remaining nine trials had unclear risk. Adequate blinding may be important to reduce bias in detection of deep vein thrombosis, pulmonary embolism, symptomatic intracranial haemorrhage, recurrent stroke, and functional outcome. Fifteen trials were double-blind, that is, treatment allocation was concealed from participants, physicians, and outcome assessors (ARGIS-1 2004; ARTSS-2 2017; Dluha 2016; Duke 1983; Duke 1986; FISS 1995; FISS-bis 1998; Liu 2020; Prins 1989; Sandset 1990; Tazaki 1986; Tazaki 1992; TOAST 1998; Turpie 1987; Vissinger 1995), and in two other trials, deep vein thrombosis was assessed 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 six-month follow-up, a 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

Twelve trials had low risk, nine trials had high risk, and the remaining seven trials had unclear risk. 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

Twenty trials had low risk, one trial had high risk, and the remaining seven trials had unclear risk. We assessed risk of bias due to missing results in syntheses of primary outcomes most important to patients and health professionals (Boutron 2021). There was no evidence of reporting bias.

Other potential sources of bias

Long-term use of antiplatelet agents

In trials with follow-up, differences in long-term use of antiplatelet treatment between 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. Aspirin was given to all patients without intracranial haemorrhage after 24 hours in Dluha 2016. Long-term treatment with aspirin was encouraged but was 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 be ruling out only substantial differences.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Anticoagulant compared to control in acute presumed ischaemic stroke

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

Twelve trials including randomised data from 22,428 participants (93.3% of participants included in the overall review) evaluated death and long-term disability. The degree of dependence was determined by noting whether 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 death or dependence at final follow up (odds ratio (OR) 0.98, 95% confidence interval (CI) 0.92 to 1.03; P = 0.37; 12 RCTs, 22,428 participants; high-certainty evidence; Analysis 1.1). However, substantial heterogeneity of treatment effect (I^2 = 64%) was evident between the different regimens included.

Subgroup analyses

By type of anticoagulant agent used

There were no significant differences in death or dependence between subgroups of different anticoagulant agents (P = 0.12; moderate-certainty evidence; Analysis 1.10).

By anticoagulant dose

There was no statistically significant difference in death or dependence at final follow-up between trials (P = 0.65; moderate-certainty evidence; Analysis 1.11).

Sensitivity analyses

Sensitivity analyses were restricted to:

- trials in which the method of randomisation ensured adequate concealment of treatment allocation, which showed that all trials evaluating death and dependence at final follow-up had adequate concealment of the randomisation process (Analysis 1.12);
- trials that restricted entry to the study to within 48 hours of stroke onset, which showed that all trials evaluating death or dependence at final follow-up enrolled participants within 48 hours of stroke onset (Analysis 1.13). Within IST 1997, there was no evidence that the effect of treatment was increased or decreased with increasing delay to randomisation up to 48 hours;
- trials other than IST 1997 (since it contained most of the data important for the review), which showed an apparent difference in effects of treatment on death or dependence at final follow-up if data from IST were included (OR 0.98, 95% CI 0.93 to 1.03; P = 0.41; 11 RCTs, 22,368 participants; high-certainty evidence; Analysis 1.1)) or excluded (OR 0.82, 95% CI.70 to 0.96; P = 0.01; 10 RCTs, 2933 participants; moderate-certainty evidence; Analysis 1.14); and
- a post-hoc sensitivity analysis to assess the impact of duration of follow-up on the estimate of effect for the primary outcome, with exclusion of the trial with assessment of the primary outcome after only one month, which had no impact on overall estimate of effect (OR 0.98, 95% CI 0.92 to 1.03; P = 0.42; 11 RCTs, 22,371 participants; high-certainty evidence; Analysis 1.15) nor on degree of heterogeneity (I^2 = 65%) (Cazzato 1989).

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

Data from 22 trials, which included randomised data from 22,602 participants (94.3% 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; P = 0.88; 22 RCTs, 22,602 participants; low-certainty evidence; Analysis 1.2). There was no significant heterogeneity (I^2 = 16%).

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

Data were available for 15 trials, which included 23,079 participants (96.1 % of participants included in the overall review). Anticoagulants were not associated with any significant reduction in the odds of death at final follow-up greater than one month (OR 1.05, 95% CI 0.98 to 1.12; P = 0.17; I^2 = 15%; 15 RCTs, 23,079 participants; moderate-certainty evidence; Analysis 1.3).

Outcome 1.4: Deep vein thrombosis during the treatment period

Ten trials, which included randomised data from 916 participants (only 3.8% of participants included in the overall review), sought to systematically determine the effect of anticoagulants on 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; P < 0.00001; 10 RCTs, 916 participants; low-certainty evidence; Analysis 1.4), although a majority of deep vein thromboses detected were subclinical and asymptomatic.

There was substantial heterogeneity between trial results (I^2 = 72%), 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), as well as 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), and 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 all other trials 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 there was no significant difference in the reduction in deep vein thrombosis from the above result if the analysis was restricted to trials in which concealment of allocation was secure (OR 0.32, 95% CI 0.15 to 0.68; I^2 = 53%; P = 0.003; 3 RCTs, 282 participants; low-certainty evidence; Analysis 1.16) or trials in which radiographic assessment was blinded (OR 0.44, 95% CI 0.27

to 0.72; I^2 = 51%; P = 0.0007; 6 RCTs, 499 participants; low-certainty evidence; Analysis 1.17). One of the trials excluded from this review did provide data on the numbers of deep vein thromboses in 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 completion of treatment.

Outcome 1.5: Recurrent ischaemic stroke or recurrent stroke of unknown pathological type during the treatment period

Twelve trials, which included 21,665 participants (90.2% 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 0.75, 95% CI 0.65 to 0.88; P =0.0003; 12 RCTs, 21,605 participants; moderate-certainty evidence; I^2 = 0, Analysis 1.5). Most data (95%) were obtained from IST 1997.

Outcome 1.6: Symptomatic intracranial haemorrhage during the treatment period

Twenty trials, which included randomised data from 23,221 participants (96.7% 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 haemorrhage more than twofold (OR 2.47, 95% CI 1.90 to 3.21; P < 0.00001; 20 RCTs, 23,221 participants; high-certainty evidence; I^2 = 0, Analysis 1.6). Most data (76%) were contributed by IST 1997.

No significant heterogeneity was apparent in the excess of haemorrhage 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 re-scanning participants who had deteriorated clinically if they were known to be receiving anticoagulants (e.g. 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 start 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 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 to 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; FISS 1995). In this trial, 25 participants (5% overall, 15 treated versus 10 control) did not have a repeat CT scan or autopsy (FISS 1995). 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 substantial reductions or increases in the risk of 'symptomatic plus asymptomatic' intracranial haemorrhage with treatment.

Outcome 1.7: 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 - i.e. each participant is counted only once, even if both events occurred, with the first event being the one that is included) is useful for assessing the net short-term effects of anticoagulants. Twelve trials, which included randomised data from 21,665 participants (90.2% 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 0.84 to 1.11; P = 0.64; 12 RCTs, 21,665 participants; moderate-certainty evidence; I^2 = 28%; Analysis 1.7). Most of the data (93.6%) were obtained from IST 1997. An analysis of recurrent stroke or intracranial haemorrhage during the follow-up period could only include data from three small studies (FISS 1995; Marshall 1960; Turpie 1987). Events were far too few for a reliable analysis.

Outcome 1.8: 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; P = 0.0009; 14 RCTs, 22,544 participants; moderate-certainty evidence; I^2 = 13.7%; Analysis 1.8).

In the trials described, the frequency of pulmonary embolism during the treatment period was variable but was 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 among 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).

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 occurred 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 1.9: 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 to require hospitalisation or transfusion). Anticoagulation was associated with a significant threefold increase in major extracranial haemorrhage (OR 2.99, 95% CI 2.24 to 3.99; P < 0.00001; 18 RCTs, 22,255 participants; moderate-certainty evidence; I^2 = 4%; Analysis 1.9).

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). Analyses with the greatest number of trials included (and hence the greatest statistical power) examined effects of treatment on death during the treatment period (Figure 4), death from all causes at final follow-up (Figure 5), and deep vein thrombosis (Figure 6). 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 positive and negative treatment effect directions (except for the outcome of deep vein thrombosis), indicating that we were unlikely to have missed a substantial number of negative trials.

Figure 4.

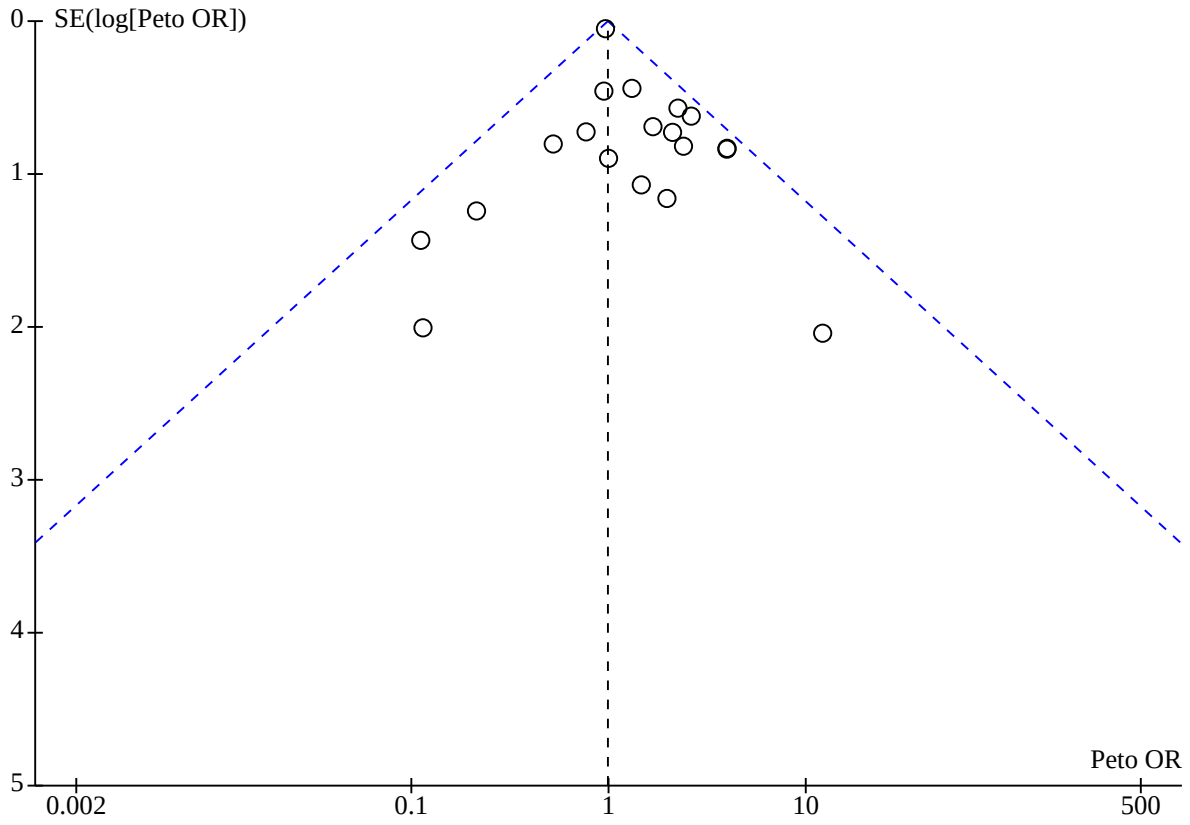


Figure 5.

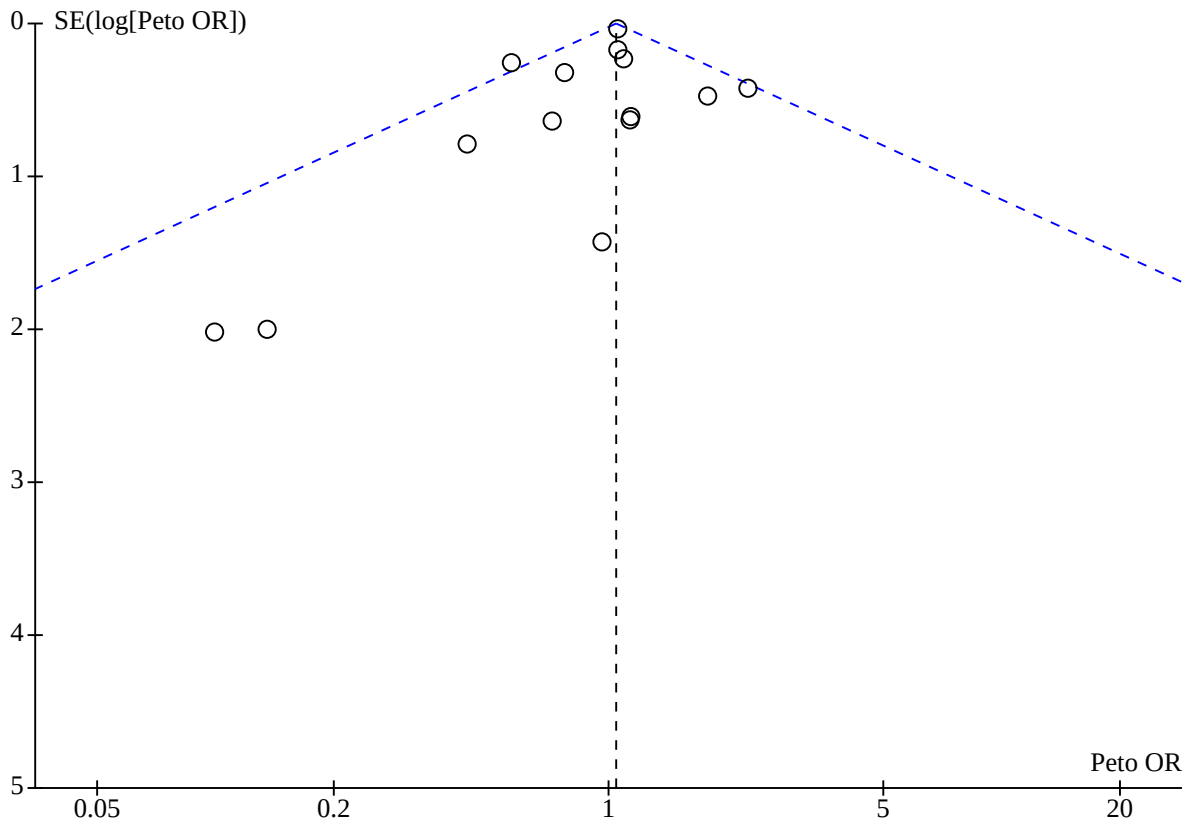
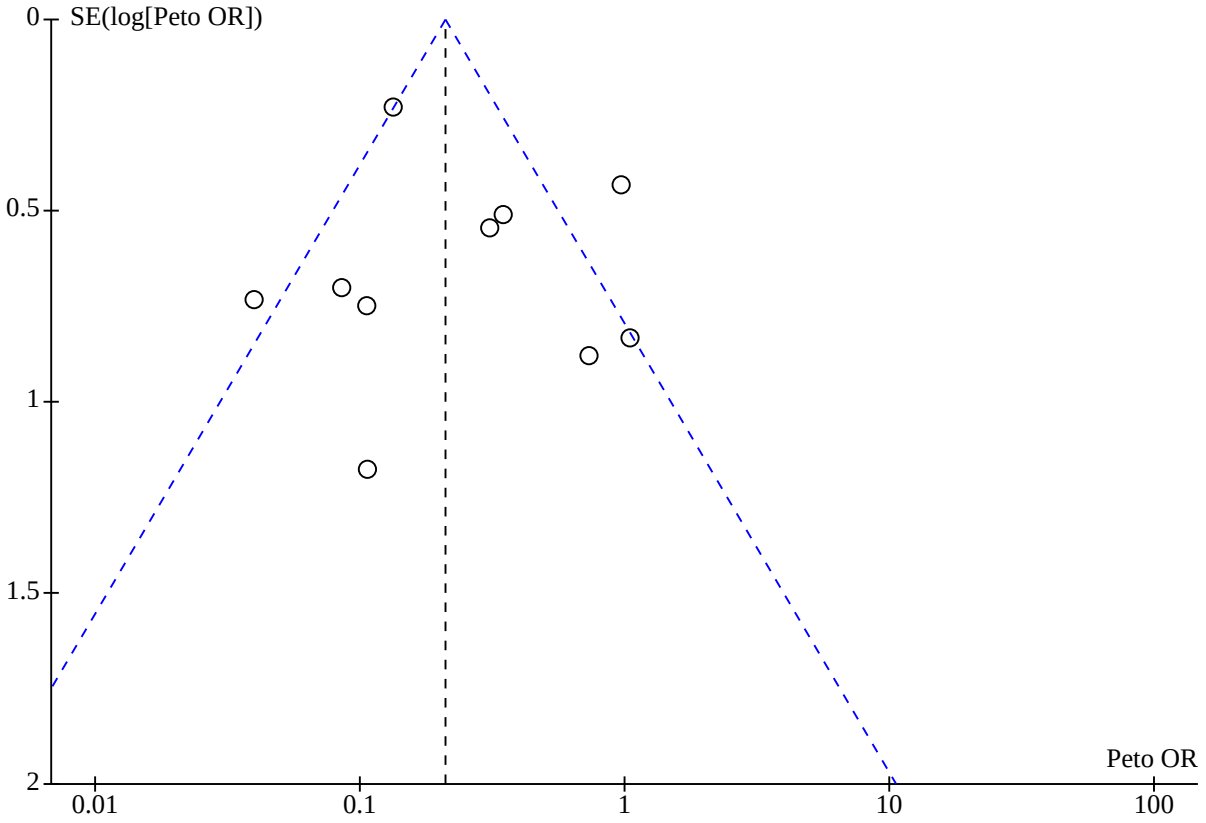


Figure 6.



DISCUSSION

The evidence provided in this updated systematic review has not changed any of the conclusions of the previous review published in 2015, and can be summarised as follows.

Summary of main results

Net effect of early anticoagulants in acute ischaemic stroke

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

Hazards of early anticoagulants in acute ischaemic stroke

To be useful, a medical therapy must be safe. Current evidence from randomised trials demonstrates a clinically and statistically significant risk of major intracranial and extracranial haemorrhage with early use of anticoagulants for people with acute ischaemic stroke.

Different anticoagulant agents - doses and routes of administration

Low-molecular-weight heparin and unfractionated intravenous heparin are not effective in reducing the risk of death or dependency, nor death, during the treatment period, or after follow-up greater than one month. Other types of agents of unfractionated subcutaneous heparin, heparinoids, and specific thrombin inhibitors have shown no significant net benefit in terms of reducing death during the treatment period, nor 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). 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

For 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 for people undergoing different types of surgery (Collins 1988). In this review, the reductions in deep vein thrombosis with acute anticoagulation were statistically significant, although this estimate is based on relatively small numbers of participants, and most of the deep vein thromboses detected were asymptomatic. Heterogeneity in the effects of

treatment is significant, which renders the overall estimate less reliable.

The clinical significance of this reduction depends critically on the control event rate. In 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 severity of stroke, presence of leg paralysis, and history of previous deep vein thrombosis (Warlow 2008). The odds of pulmonary embolism were reduced significantly (by 40%) with the use of anticoagulants. 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 number needed to treat to benefit (NNTB) was 315, although 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, 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 trials, given that 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 included 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 end of 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 numbers of deep vein thromboses and pulmonary emboli (albeit in immobile patients at higher risk), the benefit of fixed heparin regimens associated with low risk of bleeding (e.g. low fixed-dose unfractionated heparin, 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 to 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 CLOTS-3 2013 study demonstrated that for people with ischaemic and haemorrhagic stroke, intermittent pneumatic compression reduces the risk of deep vein thrombosis after stroke, without increased bleeding risk, and is effective in the presence and in the absence of background heparin therapy.

Effects on deep vein thrombosis and pulmonary embolism presented 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 involved in identifying subgroups who might have a favourable balance of risk and benefit. Although the risk of venous thromboembolism (VTE) (symptomatic plus asymptomatic) was significantly lower among participants allocated to enoxaparin, this study could not exclude a 69% increase in risk of death up to Day 14 and a 134% increase in risk of intracranial haemorrhage with enoxaparin. This is so because event rates for the more major clinical outcomes were low: among 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 for these major clinical outcomes is challenging. In conclusion, data from the present review were insufficient to reliably identify a subgroup that might benefit from use of heparin for thromboprophylaxis.

Overall completeness and applicability of evidence

This systematic review provides information about the use of anticoagulants for 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 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, 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 (Coutinho 2011; Lyrer 2010). We were reluctant to pursue further subgroup analysis because it is hazardous to explore subgroup effects when there is no significant overall effect of an intervention on major outcomes, and we had access only to major outcomes. A more detailed assessment of the effects of anticoagulants for other categories of patients (e.g. patients treated within three hours, patients with large-artery strokes, patients with carotid stenosis) would be possible with an individual patient data meta-analysis.

Stroke patients included in trials of anticoagulants to prevent deep vein thrombosis generally had quite severe strokes, and paralysis of one leg (with 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 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 because many patients are admitted to stroke units, receive aspirin, maintain good hydration, and are mobilised early.

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

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 early outcomes. The final outcome, however, was assessed at a time when patients could not accurately recall their treatment allocation, so in all likelihood, assessment of the primary outcome probably was 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. 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 of follow-up did not alter the overall estimate of effect nor reduce 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 review authors 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 include two specific recommendations that are supported by the evidence provided in this systematic review (AHA Guidelines 2019). 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 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 review 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 similarly sized increases in extracranial haemorrhage.

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 definitely increased risk of major haemorrhage. Therefore, it may be advisable to consider safer alternatives for immobile patients (such as aspirin, pneumatic 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 for the treatment of acute ischaemic stroke.

The analysis performed did not identify any category of patients who derived a 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 versus the known risk of bleeding. Evidence of benefit and safety favors aspirin as an effective antithrombotic alternative to anticoagulation 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 patients 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.

Clinicians who wish to continue to use intensive intravenous dose-adjusted heparin regimens routinely to treat specific categories of stroke patients 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 prevention of deep vein thrombosis and pulmonary embolism in stroke patients. Aspirin alone, low-dose subcutaneous heparin, and use of an intermittent pneumatic compression device are all promising possibilities, but a very large-scale randomised trial with several tens of thousands of participants would be required to determine which treatment (or which combination) offers the most favourable balance of risk and benefit for overall clinical outcomes.

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Ongoing trials

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

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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

Study characteristics	
Methods	C: randomisation not described Patient, doctor, and assessments blinded Ex during 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 vs placebo Control: aspirin used in both arms
Outcomes	Death Symptomatic ICH Major extracranial ICH Barthel Index, 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
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not clearly reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Personnel and patients blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	18% loss to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes apparently reported in the study

ARTSS-2 2017

Study characteristics

ARTSS-2 2017 *(Continued)*

Methods	C: web-based and stratified using sequential minimisation Open-label trial, outcome assessor blinded Ex during trial: none Losses to FU: 1 participant
Participants	USA and UK 90 randomised participants Mean age: 70 years, 44% female 100% CT or transcranial Doppler before entry Acute ischaemic stroke receiving IV rtPA within 4.5 hours of onset NIHSS ≥ 10 or any proximal intracranial arterial occlusion
Interventions	Rx: low-dose argatroban (infusion of 1.0 µg/kg per minute) + rtPA or high-dose argatroban (infusion of 3.0 µg/kg per minute) + rtPA Control: standard dose rtPA alone Duration: 48 hours
Outcomes	Efficacy: mRS score at day 90 Safety: sICH within 48 hours, parenchymal haematoma, haemorrhagic transformation, major systemic bleeding NIHSS neurological improvement Quality of life (EQ-5D) Economic evaluation
Notes	Ex: planned endovascular therapy FU: 90 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described that randomisation was web-based and stratified using sequential minimisation methods
Allocation concealment (selection bias)	Low risk	Web-based randomisation
Blinding (performance bias and detection bias) All outcomes	High risk	Performance bias, because personnel were not blinded
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neurologists not blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	At Day 90, 6/30, 6/31, 12/61 missing values (more than 20%), respectively, in 3 groups
Selective reporting (reporting bias)	High risk	All mentioned outcomes reported in the study

Cazzato 1989

Study characteristics	
Methods	C: random number table controlled by doctor not involved in treatment Outcome assessor blinded Ex 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) ICH (symptomatic CT) Recurrent stroke Major extracranial haemorrhage
Notes	Ex: none FU: 30 days

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method used for random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	Patients/personnel not blinded and no report on how outcome was assessed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported if this study is blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No detailed report on loss to follow-up

Cazzato 1989 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No information given

CESG 1983

Study characteristics	
Methods	C: sealed envelopes (opaque and sequentially numbered) Non-blinded Ex during trial: none Losses to FU: none
Participants	North America 45 participants Age range: 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 ICH (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**
Random sequence generation (selection bias)	Unclear risk	No description of the method used for random sequence generation
Allocation concealment (selection bias)	Low risk	Treatment randomised
Blinding (performance bias and detection bias) All outcomes	High risk	Treatment randomised but patients/personnel not blinded
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment randomised but patients/personnel not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome of review independently evaluated

CESG 1983 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reported that only 98% completed follow-up for the initial week, but no report on the following 14 days
Selective reporting (reporting bias)	Low risk	All mentioned outcomes apparently reported in the study

Chaudhary 2002

Study characteristics		
Methods	C: randomisation not described Assessment not blinded Ex during trial: none Losses to FU: none	
Participants	India 30 participants Mean age: 65 years 100% CT before entry Acute stroke - time not otherwise defined	
Interventions	Rx: parnaparin 0.3 mL subcutaneous bid for 10 days vs placebo	
Outcomes	Death and Barthel Index at 3 months	
Notes	Ex: CT with ICH, coagulopathy	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported only "prospectively randomised" with no description of sequence generation
Allocation concealment (selection bias)	Unclear risk	Concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	No blinded design reported for patients/personnel or outcome assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinded design reported for patients/personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinded design reported for outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rate of loss to follow-up

Chaudhary 2002 *(Continued)*

Selective reporting (reporting bias)	Low risk	All mentioned outcomes reported in the study

Dluha 2016

Study characteristics	
Methods	C: secure EDGAR II computer programme; computer-generated list of numbers controlled by nurses Single centre, patients and outcome assessor blinded Ex during trial: none Losses to FU: none
Participants	Slovak Republic 87 participants Mean age: 70 years, 42.5% female 100% CT before entry Acute ischaemic stroke with symptom duration at least 30 minutes, with mRS 0 to 1 and NIHSS 6 to 25 Treatment initiated within 4.5 to 24 hours since onset
Interventions	Rx: initial bolus of heparin 2500 UI and further continuous application of 1000 UI/h (18 to 20 UI/kg/h) within 24 hours, then subcutaneous nadroparin calcium Control: placebo (saline solution) within first 24 hours All patients received aspirin 100 mg daily
Outcomes	Safety: major bleeding (i.e. gastrointestinal bleeding), ICH (intracerebral, subarachnoid), death Efficacy: mRS, NIHSS, and Barthel Index were performed on 3rd, 7th, 30th, and 90th days
Notes	Ex: ICH; spontaneous rapid improvement of stroke symptoms before initiation of treatment; large ischaemia visible on initial CT covering more than 2/3 of the territory of the affected artery; epileptic seizure at onset of stroke; acute ischaemic stroke on initial CT; recent ischaemic stroke treated with IVT or planned mechanical recanalisation; stroke, myocardial infarction, or serious trauma within previous 3 months; platelet count < 100,000/mm^3; refractory hypertension; systolic pressure > 185 mmHg or diastolic pressure > 110 mmHg despite therapy; blood glucose < 2.77 or > 22.15 mmol/L; bleeding diathesis; severe liver or renal lesion; oral or parenteral anticoagulant treatment at time of stroke onset; current or previous life-threatening bleeding; major surgery within previous 3 months; malignancy; active tuberculosis; pregnancy; known heparin or nadroparin allergy; alcohol and/or drug abuse; participation in another clinical study FU: 90 days

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	List of randomised numbers (1, 2, 3) with distribution ratio 1:1:1 created by the EDGAR II computer programme
Allocation concealment (selection bias)	Low risk	Computer-based randomisation
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded design
Blinding of participants and personnel (performance bias)	Low risk	Patients not aware of type of medication they received. Clinical-state evaluator also blinded

Dluha 2016 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical-state evaluator also blinded to therapy and results of APTT
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported
Selective reporting (reporting bias)	Unclear risk	Baseline characteristics tables not provided

Duke 1983

Study characteristics		
Methods	C: random number list controlled by pharmacy Doctor, patient, and assessor blinded Ex 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 subcutaneous 8-hourly Control: placebo Duration: 7 days	
Outcomes	Death DVT (systematic I-125 scan) ICH (symptomatic) Extracranial haemorrhage	
Notes	Ex: BP > 120 diastolic, bleeding risk FU: 1 year	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Generation of random sequence not reported
Allocation concealment (selection bias)	Unclear risk	Not reported, randomised only mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded design

Duke 1983 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment blinded to patients/personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treatment blinded to outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/78 lost to follow-up at 1 year
Selective reporting (reporting bias)	Low risk	All mentioned outcomes reported

Duke 1986

Study characteristics	
Methods	C: random number list controlled by pharmacy Doctor, patient, and assessor blinded Ex during trial: none 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 < 48 hours 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) ICH
Notes	Ex: BP > 110 diastolic, coma FU: 1 year

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random tables prepared according to sex, age, and hospital
Allocation concealment (selection bias)	Low risk	Investigator doing randomisation not involved in patient evaluations
Blinding (performance bias and detection bias)	Low risk	Double-blinded design

Duke 1986 *(Continued)*

All outcomes		
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and doctors blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3/225 patients lost to follow-up
Selective reporting (reporting bias)	Low risk	All mentioned outcomes reported

Elias 1990

Study characteristics	
Methods	C: sealed envelopes (? opaque and sequentially numbered) Non-blinded Ex 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 subcutaneous 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "cette étude randomisée …"; "par randomisation, ils ont été repartis en 2 groupes ... " Translation: "this randomised study..." (p.96); "by randomisation, they [patients] have been divided in 2 groups …" (p.96)

Elias 1990 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "… un groupe de sujets traité par une dose de CY222…, et un groupe de sujets témoins non-traités..." Translation: "… a group of patients treated with a dosage of CY222 …, and a group of patients not treated …" (p.96) Probably no blinding of patient or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	High risk	Study duration: 14 days. 2/15 missing from intervention group; 1 removed on Day 4 – extensive thrombus of external carotid, 1 removed on Day 14 following diagnosis of cerebral infarct
Selective reporting (reporting bias)	Low risk	All mentioned outcomes including TVP incidence and mortality reported

FISS 1995

Study characteristics	
Methods	C: sequentially numbered boxes containing identical syringes Doctor, patient, and assessor blinded Ex during trial: 4 in Rx group (survival status known for all except 1) 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) subcutaneous (randomised between 4100 anti-Xa units 12-hourly vs 24-hourly) Control: placebo Duration: 10 days All surviving participants received aspirin 100 mg/d after 10 days
Outcomes	Death plus cause of death Functional outcome (dependency assessed by International Stroke Trial simple questions) PE (symptomatic) ICH (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

FISS 1995 *(Continued)*

	FU: 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Syringes contained in sequentially numbered boxes assigned to patients consecutively
Allocation concealment (selection bias)	Low risk	Patients randomly assigned to 1 of 3 treatments by individual investigators at each hospital
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants unaware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Personnel unaware of treatment assignment for follow-up; reviewed by another blinded observer
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/312 lost to follow-up for outcomes assessment
Selective reporting (reporting bias)	Low risk	All mentioned outcomes reported

FISS-bis 1998

Study characteristics	
Methods	C: sequentially numbered boxes Doctor, patient, and assessor blind Ex during trial: unknown Losses to FU: unknown
Participants	International 766 participants Mean age: unknown % male: unknown 100% CT before entry Ischaemic stroke with motor deficit < 24 hours since stroke onset
Interventions	Rx: nadroparin (LMWH) 86 units/kg sc once daily vs 86 units/kg subcutaneous 12-hourly Control: placebo Duration: 10 days
Outcomes	Death Functional outcome (Barthel Index score < 85 = dependent) Intracerebral haemorrhage (symptomatic CT)

FISS-bis 1998 *(Continued)*

Notes	Ex: mild stroke, coma FU: 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods used for random generation not reported
Allocation concealment (selection bias)	Unclear risk	Methods used for allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded treatment allocation to participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded treatment allocation to outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 patient lost to follow-up
Selective reporting (reporting bias)	Low risk	All mentioned outcomes reported

IST 1997

Study characteristics

Methods	C: telephone randomisation Unblinded; dependency assessment mainly blinded Ex 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: subcutaneous 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

IST 1997 *(Continued)*

	PE ICH (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
Random sequence generation (selection bias)	Low risk	Computer-allocated study treatment(s) by a minimisation algorithm used to reduce any imbalance in recorded prognostic features between treatment groups
Allocation concealment (selection bias)	Low risk	Computer-allocated study treatment(s) by a minimisation algorithm used to reduce any imbalance in recorded prognostic features between treatment groups
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Follow-up blind to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome completed by 99.99% at Day 14 and by 99.2% at 6 months
Selective reporting (reporting bias)	Low risk	All mentioned outcomes reported

Kwiecinski 1995

Study characteristics

Methods	C: unknown Blinding not stated Ex 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)

Kwiecinski 1995 *(Continued)*

	0.6 mL 12-hourly for 1 week, then 0.3 mL 12-hourly for 1 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
Random sequence generation (selection bias)	Unclear risk	No methods reported for random generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	Blinded design not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinded design not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinded design not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported during treatment period
Selective reporting (reporting bias)	Unclear risk	Abstract without full details of reporting outcomes

Liu 2020

Study characteristics

Methods	C: a centralised web-based randomisation system Doctor unblinded, assessor blinded Ex during trial: none Losses to FU: none
Participants	China 60 participants Mean age: 57 years 78% male 100% MRI before entry

Liu 2020 *(Continued)*

	4.5 to 48 hours since stroke onset
Interventions	Rx: 10 mg argatroban twice a day + standard treatment Control: standard treatment Duration: 7 days
Outcomes	Recurrent stroke Death Infection Haemorrhage of digestive tract NIHSS, mBI at 7 days and 90 days, mRS at 90 days
Notes	Ex: haemorrhagic stroke, central nervous disease, diabetes, tumour or haematological systemic disease, infection prior to stroke, antineoplastic or immune-modulating therapies FU:7 days, 90 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Enrolled patients allocated by computer in a 1: 1 ratio to control or argatroban group in a random way
Allocation concealment (selection bias)	Low risk	Centralised web-based randomisation system used for allocation concealment, with participant identifier entered before allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatment assignment known only to clinicians - not to evaluators
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment assignment known only to clinicians - not to evaluators. Each patient was clinically assessed upon enrolment (baseline), at Day 7, and day 90 after start of treatment, which was blinded to evaluators
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Each patient clinically assessed upon enrolment (baseline), at Day 7, and at Day 90 after start of treatment, which was blinded to evaluators
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data on loss to follow-up
Selective reporting (reporting bias)	Low risk	Data on all proposed outcomes reported

Marshall 1960

Study characteristics

Methods	C: unknown Non-blinded Ex during trial: none Losses to FU: none
Participants	UK

Marshall 1960 *(Continued)*

	51 participants Age range: 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 FU
Outcomes	Death but not cause of death Fatal ICH (autopsy in 8/9 deaths) Recurrent stroke Major extracranial haemorrhage
Notes	Ex: bleeding risk FU: 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods used for random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No detailed description of allocation concealment provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No detailed report provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No detailed report on blinded design provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed report provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No detailed report provided
Selective reporting (reporting bias)	Low risk	All mentioned outcomes reported

McCarthy 1977

Study characteristics

Methods	C: sealed envelopes (? opaque and sequentially numbered) DVT assessment blinded Ex during trial: none

McCarthy 1977 *(Continued)*

	Losses to FU: none
Participants	UK 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 subcutaneous 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
Random sequence generation (selection bias)	Unclear risk	Methods used for random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No clear description provided, reported only "randomly" assigned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel not blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Results done by a blinded second doctor who did not know the patients
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No detailed number of patients who completed follow-up reported
Selective reporting (reporting bias)	Low risk	Mentioned outcomes reported

McCarthy 1986

Study characteristics

Methods	C: sealed envelopes (? opaque and sequentially numbered) DVT assessment blinded

McCarthy 1986 *(Continued)*

	Ex during trial: none Losses to FU: none
Participants	UK 305 participants Mean age: 76 years 43% male No CT before entry All strokes (10% haemorrhagic on autopsy) Less than 48 hours since stroke onset
Interventions	Rx: heparin 5000 IU subcutaneous 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
Random sequence generation (selection bias)	Unclear risk	Method used for random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No detailed description provided, only mentioned "randomised"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No report on whether blinded design was used in this study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No report on whether patients were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No report on whether outcome evaluators were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rate of loss to follow-up
Selective reporting (reporting bias)	Low risk	Mentioned outcomes reported

NAT-COOP 1962

Study characteristics

NAT-COOP 1962 *(Continued)*

Methods	C: sealed envelopes (? opaque and sequentially numbered) Only patients blinded Ex 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 FU completed for all patients up to 1 month

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sealed envelopes used
Allocation concealment (selection bias)	Low risk	Patients assigned to anticoagulant or non-anticoagulant therapeutic groups on a statistically random basis by means of sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported whether this study was double-blinded
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Whether participants/personnel were blinded not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Whether outcome assessors were blinded not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No accurate number of patients who completed the study reported
Selective reporting (reporting bias)	Low risk	Outcomes mentioned in the methods reported

Pambianco 1995

Study characteristics	
Methods	C: sealed, opaque but not sequentially numbered envelopes Non-blinded Ex 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 subcutaneous 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**
Random sequence generation (selection bias)	Low risk	Sealed envelope used for randomisation
Allocation concealment (selection bias)	Low risk	Patients randomly assigned to groups in 3 clusters of 22; i.e. 22 As, 22 Bs, and 22 Cs were placed in a sealed envelope
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinded design of the study not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of treatment allocation to participants/personnel not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of treatment allocation to outcome assessor not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 175/259 completed the study; no detailed reasons provided why patients lost to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes mentioned in methods reported

Pince 1981

Study characteristics	
Methods	C: sealed envelopes (? opaque and sequentially numbered) Non-blinded Ex during trial: Rx 0, control 4 participants (2 with ICH) Losses to FU: none
Participants	France 80 participants Age range: 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 subcutaneous 8-hourly Control: no treatment Duration: 10 days
Outcomes	Death but not cause of death DVT (systematic I-125 scan) PE Major extracranial haemorrhage
Notes	Ex: bleeding risk FU: 10 days

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "l'attribution du type de traitement est faite d'après la randomisation sous enveloppe …" Translation: "attribution of treatment type is done after randomisation with sealed envelope …"
Allocation concealment (selection bias)	Low risk	Treatment and placebo groups have the same conditioning and the same posology
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo et antiagrégants sont pour nous indiscernables ..." Translation: "placebo and antiaggregant are indistinguishable for us [the personnel] …"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given on blinded assessment of outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	9/120 patients excluded

Pince 1981 *(Continued)*

Selective reporting (reporting bias)	Low risk	Mentioned outcomes of frequency of phlebitis, side effects of treatments, and clinical evolution in function of treatment reported

Prins 1989

Study characteristics	
Methods	C: sequentially numbered identical syringes Double-blinded Ex during trial: none Losses to FU: none
Participants	The 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 subcutaneous 12- hourly Control: placebo Duration: 14 days
Outcomes	Death plus cause of death DVT (systematic I-125 scan with venography) PE ICH (symptomatic plus systematic CT) Major extracranial haemorrhage
Notes	Ex: coma FU: 14 days

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No report on method used for randomisation generation
Allocation concealment (selection bias)	Unclear risk	No report on method used for allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Tested using a double-blind, placebo-controlled, randomised trial design. with 30 patients allocated to each group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Mentioned double-blinded

Prins 1989 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No report of loss to follow-up during 14 days
Selective reporting (reporting bias)	Unclear risk	Abstract with no detailed information

Sandset 1990

Study characteristics	
Methods	C: sequentially numbered identical ampoules Doctor, patient, and assessor blinded Ex during trial: none Losses to FU: none
Participants	Norway 103 participants Age range: 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 subcutaneous 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) ICH (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**
Random sequence generation (selection bias)	Unclear risk	Only mentioned 'randomised' without description of methods used
Allocation concealment (selection bias)	Unclear risk	Only mentioned 'randomised' without description of methods used
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blinded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blinded

Sandset 1990 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 42/52 patients in the intervention group being followed up for DVT
Selective reporting (reporting bias)	Low risk	Outcomes mentioned in methods reported

Sarma 2003

Study characteristics	
Methods	C: computer-generated randomisation table Blinding not clear Ex during trial: none Losses to FU: none
Participants	India 40 participants Mean age: 63 years 32% female 100% CT before entry Acute ischaemic stroke Less than 24 hours since onset
Interventions	Rx: combination of subcutaneous nadroparin 4100 units and aspirin 325 mg per day Control: aspirin 325 mg per day alone Nadroparin stopped after 10 days of therapy and aspirin continued for 4 weeks
Outcomes	Neurological status (using the Mathew Scale) Haemorrhagic transformation
Notes	Ex: haemorrhagic infarction, active peptic ulcer, recent head trauma or haemorrhagic stroke in preceding 3 months, GI or urinary tract haemorrhage in preceding 3 weeks or blood pressure > 185/120 mmHg FU: 4 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details on method used for random generation reported
Allocation concealment (selection bias)	Unclear risk	No detailed description of randomisation provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details on blinding design reported
Blinding of participants and personnel (performance bias)	Unclear risk	No details on blinding design reported

Sarma 2003 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details on blinding design reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not reported
Selective reporting (reporting bias)	High risk	Selective adverse events reported

Tazaki 1986

Study characteristics	
Methods	C: numbered or coded containers administered sequentially to enrolled participants Doctor, patient, and assessor blinded Ex during trial: none Losses to FU: none
Participants	Japan 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/d vs 30 mg/d continuous iv for 2 days; then 20 mg 12 hourly IV for 5 days Control: placebo All patients received glycerol 500 mg/d 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**
Random sequence generation (selection bias)	Unclear risk	Methods used for randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Methods used for allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double-blinded' mentioned

Tazaki 1986 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double-blinded' design used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double-blinded' design used
Incomplete outcome data (attrition bias) All outcomes	High risk	42/156 not analysed at 28 days; no reasons provided
Selective reporting (reporting bias)	Unclear risk	Abstract: lack of information

Tazaki 1992

Study characteristics	
Methods	C: numbered or coded containers administered sequentially to enrolled patients Doctor, patient, and assessor blinded Ex during trial: none Losses to FU: none
Participants	Japan 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/d for 2 days (continuous IV), then MD805 20 mg 12-hourly for 5 days (IV) Control: placebo All groups received glycerol 500 mL/d for 7 days Duration: 7 days
Outcomes	Death Functional outcome ICH (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
Random sequence generation (selection bias)	Unclear risk	Method used for random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method used for allocation concealment not described

Tazaki 1992 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	'Double-blinded' design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double-blinded' design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double-blinded' design
Incomplete outcome data (attrition bias) All outcomes	High risk	118/138 analysed at the end; no reasons provided for the 20 patients excluded
Selective reporting (reporting bias)	Unclear risk	Abstract in translation: lack of information

TOAST 1998

Study characteristics	
Methods	C: permuted blocks with randomly ordered sizes of 6, 6, and 4; randomisation lists pharmacy controlled Doctor, patient, and assessor blinded Ex during trial: none Losses to FU: 25 participants (11 treatment, 14 control)
Participants	USA 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 ≥ 12
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 ICH (symptomatic CT) Extracranial haemorrhage
Notes	Ex: age < 18 or > 85, women of childbearing potential, severe stroke (NIHSS score > 15), weight < 125 pounds FU: 7 days and 3 months
Risk of bias	
Bias	**Authors' judgement** / **Support for judgement**

TOAST 1998 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomised 1:1 to treatment with ORG 10172 or placebo using permuted blocks with randomly ordered sizes and balanced for every 16 consecutive patients
Allocation concealment (selection bias)	Low risk	Randomised using permuted blocks
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind design
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/646 in treatment and 5/635 in control lost to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes mentioned in methods reported

Turpie 1987

Study characteristics	
Methods	C: sequentially numbered identical containers Double-blind Ex during trial: none Losses to FU: none
Participants	Canada 75 participants Age range: 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 subcutaneous 12-hourly Control: placebo Duration: 14 days or prior to discharge Antiplatelet therapy during follow-up not reported
Outcomes	Death plus cause of death DVT (systematic I-125 scan + plethysmography with venography) PE (symptomatic) ICH (symptomatic CT) Extracranial haemorrhage Recurrent stroke

Turpie 1987 *(Continued)*

Notes	Ex: bleeding risk FU: 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported how randomisation was generated
Allocation concealment (selection bias)	Low risk	Patients allocated according to a prescribed randomised arrangement to Org 10172 prophylaxis or saline placebo
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, trial nurses, and attending physicians unaware of treatment regimen for each patient
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, trial nurses, and attending physicians unaware of treatment regimen for each patient
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors unaware of treatment regimen for each patient
Incomplete outcome data (attrition bias) All outcomes	Low risk	8/75 did not complete the study; reasons provided
Selective reporting (reporting bias)	Low risk	Mentioned outcomes reported

Vissinger 1995

Study characteristics

Methods	C: coded containers administered sequentially to enrolled participants Doctor, patient, and assessor blinded Ex 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)

Vissinger 1995 *(Continued)*

	PE (symptomatic)
Notes	Ex 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
Random sequence generation (selection bias)	Low risk	Randomisation held by pharmacy
Allocation concealment (selection bias)	Unclear risk	Not provided
Blinding (performance bias and detection bias) All outcomes	High risk	Double-blind design not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Identical pre-packed injections; unblinded to personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinded assessment for outcome not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	13/20 lost to follow-up at the end
Selective reporting (reporting bias)	Unclear risk	No information given

ADL: activities of daily living
APTT: activated partial thromboplastin time
BP: blood pressure
C: concealment
CSF: cerebrospinal fluid
CT: computed tomography
DVT: deep vein thrombosis
EQ-5D: EuroQol - 5 Dimension
Ex: exclusion
FU: follow-up
GI: gastrointestinal
ICH: intracranial haemorrhage
IM: intramuscular
IV: intravenous
IVT: intravenous thrombolysis
LMWH: low-molecular-weight heparin
LP: lumbar puncture
mBI: modified Barthel Index
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
OHS: Oxford Handicap Scale
PE: pulmonary embolism

PT: prothrombin time
rtPA: recombinant tissue plasminogen activator
Rx: treatment
sICH: symptomatic intracranial haemorrhage

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

Study	Reason for exclusion
Afshari 2015	Not an RCT
Amarenco 2014	Participants randomised within 14 days of stroke onset
Asberg 2018	Comparison of 2 anticoagulant regimens
Bergmann 1996	Not all participants had AIS
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
Chang 2002	No published data available
Chen 2019	Comparison of 2 anticoagulant regimens
ChiCTR-OIN-17013510	Not an RCT
COU 9116	Participants randomised within 14 days of stroke onset
Coutinho 2015	No anticoagulant
Crepin-leblond 1994	Comparison of 2 anticoagulant regimens
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
DATAS II 2020	Comparison of anticoagulant and antiplatelet
Dehen 1994	Control group received low-molecular-weight heparin plus placebo
Diener 2005	Comparison of 2 anticoagulant regimens
Dong 2003	No published data available
Donnan 1996	No anticoagulant
Dumas 1994	Comparison of 2 anticoagulant regimens
Egan 1999	Not an RCT
Egberts 1996	No published data available

Study	Reason for exclusion
ELAN 2017	Does not compare effects of anticoagulants
EMT 1992	Not an RCT
Enger 1965	Time from stroke to treatment unclear
England 2010	Not an RCT
Eriksson 1983	Non-random: allocation by month of admission
Fang 2015	Study not conducted
Fassbender 1998	Comparison of 2 anticoagulant regimens
Field 2017	No published data available
Fradley 2014	Comparison of 2 anticoagulant regimens
Geisler 2017	Anticoagulant vs antiplatelet regimen
Gelmers 1980	Non-random: alternate allocation
Grond 2000	Not an RCT
HAEST 2000	Anticoagulant vs antiplatelet regimen
Hillbom 1999	Comparison of 2 anticoagulant regimens
Hillbom 2002	Comparison of 2 anticoagulant regimens
Hossman 1986	No published data available
Hui 2016	No published data available
IRCT2014020213698N1	Comparison of 2 anticoagulant regimens
IRCT201407213106N18	No anticoagulant
ISRCTN25644448	Participant randomisation within 14 days of stroke onset
Ji 2017	Comparison of 2 anticoagulant regimens
Jin 2017	Comparison of 2 anticoagulant regimens
JPRN-UMIN000014405	Did not explore the effect of anticoagulant
JPRN-UMIN000025392	Randomisation over 14 days
Kamel 2018	Participants randomised within 14 days of stroke onset
Kang 2010	No clinical outcome data provided
Kario 1995	No clinically relevant outcomes reported
Kataoka 2000	Not an RCT

Study	Reason for exclusion
Kim 2003	Comparison of 2 anticoagulant regimens
Kobayashi 1997	No clinically relevant outcomes reported
Lee 1994	Confounded with urokinase
Lee 2008	Comparison of 2 anticoagulant regimens
Lee 2014	Did not involve anticoagulant as an intervention
Liu 2015	Anticoagulant vs antiplatelet regimen
Lu 2001	No published data available
Luo 2013	Comparison of 2 anticoagulant regimens
McCarthy 1993	Data not available despite repeated contact with study authors
McDevitt 1959	Time from stroke to treatment unclear
Melero 2007	Comparison of 2 anticoagulant regimens
Meredit 2009	Comparison of 2 anticoagulant regimens
Moulin 1994	Comparison of 2 anticoagulant regimens
Muck 1997	Comparison of 2 anticoagulant regimens
NAVIGATE ESUS 2014	Randomised between 7 days and 6 months after stroke onset
NCT01924325	Anticoagulant vs antiplatelet regimen
NCT02221102	Study not conducted
NCT02283294	Anticoagulant vs antiplatelet regimen
NCT03961334	Anticoagulant vs antiplatelet regimen
OPTIMAS 2018	Does not compare effect of anticoagulant but time of commencing anticoagulant
PREVAIL 2004	Comparison of 2 anticoagulant regimens
RAPID 2005	Anticoagulant vs antiplatelet regimen
RESPECT CVT 2018	Randomisation 5 to 15 days after initial acute treatment
RE-SPECT ESUS 2019	Recruitment within 6 months of embolic stroke onset
Rha 2001	No published data available
Rose 2019	Comparison of 2 anticoagulant regimens
Rosin 1994	Data not available despite repeated contact with study authors
Shi 2004	No clinically relevant outcomes reported

Study	Reason for exclusion
SOCRATES 2016	Anticoagulant not an intervention
Stiekema 1988	No control group: dose-finding trial
TAIST 2001	Anticoagulant vs antiplatelet regimen
Tan 1998	Not randomised; no clinically relevant outcomes reported
Thygesen 1964	Non-random allocation
Tomek 2011	Comparison of 2 anticoagulant regimens
Toni 2000	Not an RCT
Trencev 2008	No published data available
Triple AXEL 2015	Comparison of 2 anticoagulant regimens
Tsuchiya 1989	Confounded with urokinase
Tsuchiya 1990	Confounded with urokinase
Turpie 1991	Comparison of 2 anticoagulant regimens
Turpie 1992	Comparison of 2 anticoagulant regimens
VA Study 1961	Treatment started acutely in only 50%; unable to get individual patient data for just these participants
Warach 2003	No published data available
Wellington 2002	Comparison of 2 anticoagulant regimens
Wong 2000	Comparison of 2 anticoagulant regimens
Yamaguchi 2004	Comparison of 2 anticoagulant regimens
Yang 2016	Anticoagulant not an intervention
Yi 2015	Anticoagulant vs antiplatelet regimen
Zhang 2005	Not clearly randomised
Zhu 2014	No published data available
Zuo 2017	Anticoagulant not an intervention

AIS: acute ischaemic stroke
RCT: randomised controlled trial

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

ChiCTR1800018313

Study name	A multicenter trial for revascularization pretreated with argatroban for acute ischemic stroke
Methods	Randomised parallel controlled trial
Participants	Age 18 to 80 years, NIHSS < 30, ASPECTS > 6, CTA/DSA/MRA confirmed large vascular (internal carotid artery, vascular anomalies, basilar artery, the second segments of the middle cerebral artery) Time from attack to randomisation < 8 hours Estimated 300 participants China
Interventions	Argatroban treatment vs placebo
Outcomes	Functional outcomes: mRS at 90 days
Starting date	10 October 2018
Contact information	Junhui Chen; chenjunhui101@163.com
Notes	http://www.chictr.org.cn/showproj.aspx?proj=30871

ISRCTN76741621

Study name	Multicentre randomised clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: the effect of periprocedural medication: heparin, antiplatelet agents, both or neither
Methods	Multi-centre phase III clinical trial with randomised treatment allocation, open-label treatment, and blinded endpoint assessment (PROBE), with a 2 × 3 factorial design (treatment)
Participants	Age ≥ 18 years, acute ischaemic stroke caused by intracranial large vessel occlusion of anterior circulation with intra-arterial treatment (groin puncture) possible within 0 to 6 hours Estimated 1500 participants The Netherlands
Interventions	Acetylsalicylic acid, unfractionated heparin, both or none during intra-arterial treatment Acetylsalicylic acid will be administered intravenously, at a loading dose of 300 mg Unfractionated heparin will be administered IV at a low dose (loading dose of 5000 IU followed by 500 IU/hour × 6 hours) or a moderate dose (loading dose of 5000 IU followed by 1250 IU/hour × 6 hours) Both IV acetylsalicylic acid and heparin treatment should be started prior to groin puncture when no IVT is administered, or directly after/when IV alteplase has been stopped Duration of anticoagulation 6 hours
Outcomes	mRS at 90 days
Starting date	01 November 2017
Contact information	Rob van de Graaf, University Medical Center's Gravendijkwal 230, Departments of Neurology and Radiology, Room Ee 2240, 3000 CA, Rotterdam, The Netherlands
Notes	http://www.isrctn.com/ISRCTN76741621

NCT03506009

Study name	Argatroban Plus R-tPA for Acute Posterior Circulation Infarction (AR-PCI): a prospective, random, blinded assessment of outcome and open label multi-center study
Methods	Prospective, random, blinded assessment of outcome and open-label multi-centre study
Participants	18 to 80 years of age, posterior circulation, ischaemic stroke, NIHSS 4 to 25, time from onset to treatment ≤ 6 hours
Interventions	Rx: argotroban + rt-PA vs rt-PA only; acute ischaemic stroke
Outcomes	mRS at 90 days Early neurological deterioration, NIHSS Occurrence of stroke Symptomatic intracranial hemorrhage within 36 hours
Starting date	11 July 2018
Contact information	Hui-Sheng Chen, General Hospital of Shenyang Military Region
Notes	https://clinicaltrials.gov/ct2/show/NCT03506009

NCT03570281

Study name	Edoxaban for the treatment of coagulopathy in patients with active cancer and acute ischemic stroke: a pilot study (ENCHASE)
Methods	Allocation: randomised Intervention model: parallel assignment Masking: none (open-label) Primary purpose: treatment
Participants	40
Interventions	Edoxaban vs enoxaparin
Outcomes	Primary outcome: interval change of serum D-dimer level between days 0 and 7 Secondary outcomes: number of microembolic signals detected by transcranial doppler, mRS at 90 days from 0 to 6 (higher is worse), symptomatic intracerebral haemorrhage, major bleeding, all-cause death
Starting date	26 June 2018
Contact information	neuroboy50@naver.com
Notes	

NCT03735979

Study name	Multi-arm Optimization of Stroke Thrombolysis (MOST): a single blinded, randomized controlled adaptive, multi-arm, adjunctive-thrombolysis efficacy trial in ischemic stroke
Methods	Double-blinded (participant, outcomes assessor blinded)

NCT03735979 *(Continued)*

Participants	18 years of age and older, acute ischaemic stroke treated with 0.9 mg/kg IV rt-PA within 3 hours of stroke onset or time last known well, NIHSS score ≥ 6 prior to IV rt-PA, able to receive assigned study drug within 60 minutes of initiation of IV rt-PA Estimated 1200 participants USA
Interventions	Argatroban: 100 µg/kg bolus followed by 3 µg/kg per minute for 12 hours Eptifibatide: 135 µg/kg bolus followed by 0.75 µg/kg per minute infusion for 2 hours Control: placebo
Outcomes	Efficacy: mRS at 90 days
Starting date	15 October 2019
Contact information	Opeolu Adeoye; adeoyeo@ucmail.uc.edu Andrew Barreto Andrew; d.barreto@uth.tmc.edu University of Cincinnati, National Institute of Neurological Disorders and Stroke
Notes	https://clinicaltrials.gov/ct2/show/NCT03735979

NCT03740958

Study name	Argatroban plus R-tPA for acute ischemic stroke: a prospective, random, open label, blinded assessment of outcome multi-center study
Methods	Multi-centre, prospective, randomised, open-label, blind-endpoint trial
Participants	Patients with acute ischaemic stroke, NIHSS score ≥ 6 at time of randomisation, within 4.5 hours of symptom onset
Interventions	Argatroban (100 µg/kg bolus followed by infusion of 1.0 µg/kg per minute for 48 hours) plus r-tPA or r-tPA alone
Outcomes	Proportion of patients with excellent outcome of no clinically significant residual stroke deficits (mRS 0 to 1) at 90 days
Starting date	21 December 2018
Contact information	Contact: Xinhong Wang; Doctor15309885658 ext 024-28897512450341972@qq.com Contact: Yu Cui; Master18842398646 ext 024-28897512314486939@qq.com
Notes	

NCT04275180

Study name	Clinical study of argatroban in the treatment of acute progressive ischemic stroke
Methods	Randomised parallel open-label
Participants	Progress of ischaemic stroke with neurological function deteriorated from 6 hours to 48 hours after onset of the disease, NIHSS score increased by ≥ 2 points Estimated 628 participants China

NCT04275180 *(Continued)*

Interventions	Argatroban on the basis of standard medical treatment Control: standard medical treatment, including routine antiplatelet, blood pressure control, statins to stabilise plaque, etc
Outcomes	Efficacy: mRS at 3 months; NIHSS at 7 days, 1 month, and 3 months Safety: SICH at 7 days, adverse events at 3 months
Starting date	21 March 2020
Contact information	Min Lou, Loumingxc@vip.sina.com, Second Affiliated Hospital, School of Medicine, Zhejiang University
Notes	https://clinicaltrials.gov/ct2/show/study/NCT04275180

NCT04304508

Study name	NCT04304508
Methods	Double-blinded (participant, care provider, investigator, outcomes assessor blinded)
Participants	45 years of age and older Non-cardioembolic ischaemic stroke Estimated 1800 participants: Australia, Austria, Belgium, Bulgaria, Canada, China, Czechia, Denmark, Finland, Germany, Hungary, Italy, Japan, Netherlands, Poland, Portugal, Russian Ferderation, Slovakia, Spain, Sweden, Switzerland, UK, USA
Interventions	Oral FXIa inhibitor: BAY2433334 compared to placebo Tablet, taken orally once a day
Outcomes	Safety: major bleeding and clinically relevant non-major (CRNM) bleeding; symptomatic ischaemic stroke or covert brain infarcts; death; adverse events
Starting date	15 June 2020
Contact information	Bayer Clinical Trials Contact clinical-trials-contact@bayer.com
Notes	https://clinicaltrials.gov/ct2/show/study/NCT04304508

ASPECTS: Alberta Stroke Programme Early CT Score
CTA: computed tomography angiography
DSA: digital subtraction angiography
IV: intravenous
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
rt-PA: recombinant tissue plasminogen activator
Rx: treatment
sc: subcutaneous
SICH: symptomatic intracerebral hemorrhage

DATA AND ANALYSES

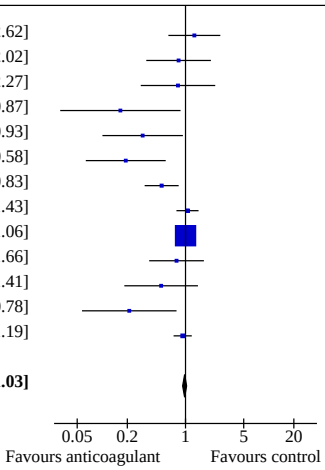
Comparison 1. Anticoagulant vs control in acute presumed ischaemic stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Dead or dependent at end of follow-up (if > 1 month)	12	22428	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.92, 1.03]
1.2 Death from all causes during treatment period	22	22602	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.90, 1.09]
1.3 Death from all causes at final follow-up (if > 1 month)	15	23079	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.98, 1.12]
1.4 Deep vein thrombosis during treatment period	10	916	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.21 [0.15, 0.29]
1.5 Recurrent ischaemic or unknown stroke during treatment period	12	21665	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.65, 0.88]
1.6 Symptomatic intracranial haemorrhage during treatment period	20	23221	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.47 [1.90, 3.21]
1.7 Any recurrent stroke or symptomatic intracranial haemorrhage during treatment period or follow-up (> 1 month)	12	21665	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.84, 1.11]
1.8 Symptomatic pulmonary embolism during treatment period	14	22544	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.44, 0.81]
1.9 Major extracranial haemorrhage during treatment period	18	22255	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.99 [2.24, 3.99]
1.10 Subgroup analysis by type of anticoagulant agent used: effect on death or dependency	12	22428	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.92, 1.03]
1.10.1 Unfractionated heparin (subcutaneous) versus control	1	19435	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.94, 1.06]
1.10.2 Low-molecular-weight heparin versus control	6	1328	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.59, 0.93]
1.10.3 Heparinoid (subcutaneous) versus control	1	57	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.29, 2.29]
1.10.4 Heparinoid (intravenous) versus control	2	1329	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.12]
1.10.5 Direct thrombin inhibitor versus control (intravenous)	3	279	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.55, 1.48]
1.11 Subgroup analysis by anticoagulant dose: effect on death or dependency	11	22339	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.93, 1.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11.1 Adjusted full-dose intravenous anticoagulant	4	1522	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.70, 1.11]
1.11.2 Medium fixed-dose anticoagulant	4	10361	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.91, 1.06]
1.11.3 Low fixed-dose anticoagulant	7	10456	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.91, 1.07]
1.12 Sensitivity analysis: dead or dependent at end of follow-up (if > 1 month) in trials with adequate concealment of treatment allocation	6	21286	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.92, 1.03]
1.13 Sensitivity analysis: dead or dependent at end of follow-up (if > 1 month) for patients within 48 hours of stroke onset	11	22298	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.89, 1.00]
1.14 Sensitivity analysis: dead or dependent at end of follow-up (if > 1 month) excluding IST3 trial	11	2993	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.69, 0.95]
1.15 Sensitivity analysis: dead or dependent at end of follow-up (if > 1 month) excluding trial with assessment of primary outcome after only 1 month	11	22371	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.92, 1.03]
1.16 Sensitivity analysis: deep vein thrombosis during treatment period restricted to trials where concealment of allocation was secure	3	282	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.16, 0.71]
1.17 Sensitivity analysis: deep vein thrombosis during treatment period restricted to trials where radiographic assessment was blinded	6	499	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.27, 0.72]

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

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F G H
ARGIS-1 2004	43	83	21	46	0.6%	1.28 [0.62 , 2.62]	? ? + + + - +
ARTSS-2 2017	35	61	18	29	0.4%	0.83 [0.34 , 2.02]	+ + - - + - -
Cazzato 1989	13	28	15	29	0.3%	0.81 [0.29 , 2.27]	? ? - - - ? ?
Chaudhary 2002	1	15	6	15	0.1%	0.17 [0.03 , 0.87]	? ? - - - + +
Dluha 2016	6	27	13	26	0.2%	0.31 [0.10 , 0.93]	+ + + + + + ?
Dluha 2016	5	34	13	26	0.2%	0.19 [0.06 , 0.58]	+ + + + + + ?
FISS 1995	100	207	68	105	1.3%	0.52 [0.32 , 0.83]	+ + + + + + +
FISS-bis 1998	300	516	142	250	3.2%	1.06 [0.78 , 1.43]	? ? + + + + +
IST 1997	6063	9717	6062	9718	88.0%	1.00 [0.94 , 1.06]	+ + ? - + + +
Kwiecinski 1995	19	62	21	58	0.5%	0.78 [0.37 , 1.66]	? ? - - - + ?
Liu 2020	10	30	15	30	0.3%	0.51 [0.18 , 1.41]	+ + + + + ? +
Sarma 2003	3	20	10	20	0.2%	0.21 [0.06 , 0.78]	? ? ? ? ? ? -
TOAST 1998	159	641	167	635	4.7%	0.92 [0.72 , 1.19]	+ + + + + + +
Total (95% CI)		**11441**		**10987**	**100.0%**	**0.98 [0.92 , 1.03]**	
Total events:	6757		6571				



Heterogeneity: Chi² = 33.05, df = 12 (P = 0.0010); I² = 64%
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

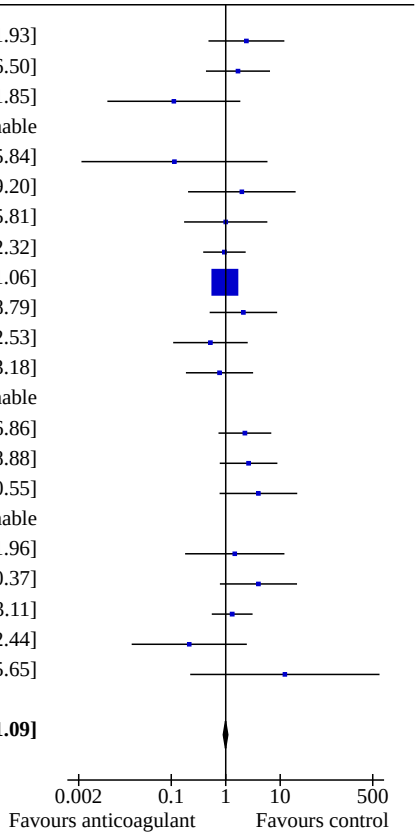
Analysis 1.2. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 2: Death from all causes during treatment period

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARGIS-1 2004	6	118	1	58	0.3%	2.40 [0.48 , 11.93]
Cazzato 1989	6	28	4	29	0.5%	1.68 [0.43 , 6.50]
CESG 1983	0	24	2	21	0.1%	0.11 [0.01 , 1.85]
Chaudhary 2002	0	15	0	15		Not estimable
Duke 1983	0	35	1	30	0.1%	0.11 [0.00 , 5.84]
Duke 1986	2	112	1	113	0.2%	1.98 [0.20 , 19.20]
Elias 1990	3	15	3	15	0.3%	1.00 [0.17 , 5.81]
FISS 1995	15	207	8	105	1.1%	0.95 [0.39 , 2.32]
IST 1997	876	9717	905	9718	92.7%	0.96 [0.88 , 1.06]
Marshall 1960	6	26	3	25	0.4%	2.11 [0.51 , 8.79]
McCarthy 1977	3	16	5	16	0.4%	0.52 [0.11 , 2.53]
NAT-COOP 1962	6	15	7	15	0.4%	0.77 [0.19 , 3.18]
Pambianco 1995	0	64	0	67		Not estimable
Pince 1981	10	40	5	40	0.7%	2.25 [0.74 , 6.86]
Prins 1989	9	30	4	30	0.6%	2.63 [0.78 , 8.88]
Sandset 1990	5	52	1	51	0.3%	3.98 [0.77 , 20.55]
Sarma 2003	0	20	0	20		Not estimable
Tazaki 1986	3	104	1	52	0.2%	1.47 [0.18 , 11.96]
Tazaki 1992	5	69	1	69	0.3%	3.99 [0.78 , 20.37]
TOAST 1998	12	646	9	635	1.2%	1.31 [0.55 , 3.11]
Turpie 1987	1	50	2	25	0.1%	0.21 [0.02 , 2.44]
Vissinger 1995	1	20	0	30	0.1%	12.18 [0.22 , 665.65]
Total (95% CI)		**11423**		**11179**	**100.0%**	**0.99 [0.90 , 1.09]**
Total events:	969		963			

Heterogeneity: Chi² = 21.38, df = 18 (P = 0.26); I² = 16%

Test for overall effect: Z = 0.15 (P = 0.88)

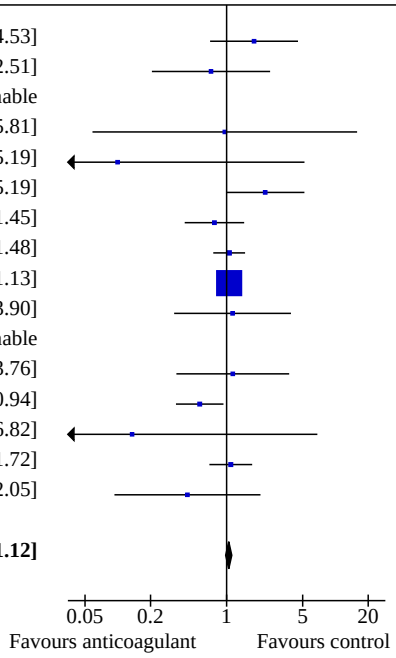
Test for subgroup differences: Not applicable



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

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARGIS-1 2004	18	118	5	58	0.5%	1.79 [0.71 , 4.53]
ARTSS-2 2017	8	61	5	29	0.3%	0.72 [0.21 , 2.51]
Chaudhary 2002	0	15	0	15		Not estimable
Dluha 2016	1	27	1	26	0.1%	0.96 [0.06 , 15.81]
Dluha 2016	0	34	1	26	0.0%	0.10 [0.00 , 5.19]
Duke 1986	17	112	8	113	0.6%	2.26 [0.99 , 5.19]
FISS 1995	32	207	20	105	1.0%	0.77 [0.41 , 1.45]
FISS-bis 1998	146	516	68	250	3.7%	1.06 [0.75 , 1.48]
IST 1997	2165	9717	2076	9718	89.4%	1.06 [0.99 , 1.13]
Kwiecinski 1995	6	62	5	58	0.3%	1.13 [0.33 , 3.90]
Liu 2020	0	30	0	30		Not estimable
Marshall 1960	8	26	7	25	0.3%	1.14 [0.35 , 3.76]
McCarthy 1986	31	144	53	161	1.6%	0.57 [0.34 , 0.94]
Sarma 2003	0	20	1	20	0.0%	0.14 [0.00 , 6.82]
TOAST 1998	42	646	38	635	2.0%	1.09 [0.69 , 1.72]
Turpie 1987	4	50	4	25	0.2%	0.44 [0.09 , 2.05]
Total (95% CI)		**11785**		**11294**	**100.0%**	**1.05 [0.98 , 1.12]**
Total events:	2478		2292			

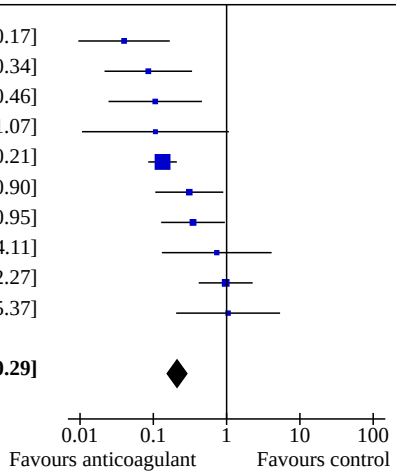
Heterogeneity: Chi² = 15.34, df = 13 (P = 0.29); I² = 15%
Test for overall effect: Z = 1.36 (P = 0.17)
Test for subgroup differences: Not applicable



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

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Elias 1990	0	15	12	15	4.6%	0.04 [0.01 , 0.17]
McCarthy 1977	2	16	12	16	5.0%	0.09 [0.02 , 0.34]
Turpie 1987	2	50	7	25	4.4%	0.11 [0.02 , 0.46]
Duke 1983	0	35	3	30	1.8%	0.11 [0.01 , 1.07]
McCarthy 1986	32	144	117	161	46.8%	0.13 [0.09 , 0.21]
Prins 1989	6	27	15	30	8.3%	0.31 [0.11 , 0.90]
Pince 1981	7	40	14	36	9.4%	0.35 [0.13 , 0.95]
Vissinger 1995	2	20	4	30	3.2%	0.73 [0.13 , 4.11]
Sandset 1990	15	45	17	50	13.1%	0.97 [0.42 , 2.27]
Pambianco 1995	3	64	3	67	3.5%	1.05 [0.20 , 5.37]
Total (95% CI)		**456**		**460**	**100.0%**	**0.21 [0.15 , 0.29]**
Total events:	69		204			

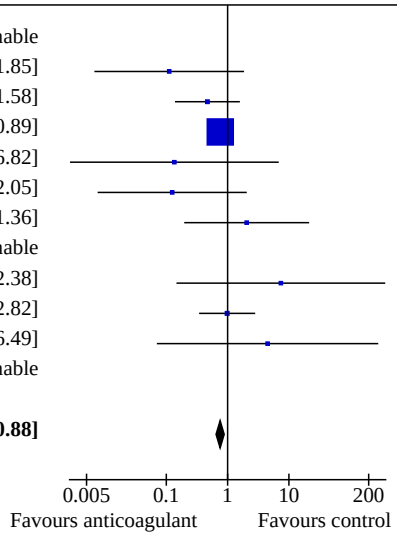
Heterogeneity: Chi² = 31.61, df = 9 (P = 0.0002); I² = 72%
Test for overall effect: Z = 9.94 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 5: Recurrent ischaemic or unknown stroke during treatment period

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Cazzato 1989	0	28	0	29		Not estimable
CESG 1983	0	24	2	21	0.3%	0.11 [0.01 , 1.85]
FISS 1995	6	207	6	105	1.6%	0.47 [0.14 , 1.58]
IST 1997	283	9717	370	9718	94.9%	0.76 [0.65 , 0.89]
Liu 2020	0	30	1	30	0.2%	0.14 [0.00 , 6.82]
Marshall 1960	0	26	2	25	0.3%	0.12 [0.01 , 2.05]
NAT-COOP 1962	2	15	1	15	0.4%	2.05 [0.20 , 21.36]
Pambianco 1995	0	64	0	67		Not estimable
Tazaki 1992	1	69	0	69	0.2%	7.39 [0.15 , 372.38]
TOAST 1998	7	646	7	635	2.1%	0.98 [0.34 , 2.82]
Turpie 1987	1	50	0	25	0.1%	4.48 [0.07 , 286.49]
Vissinger 1995	0	20	0	30		Not estimable
Total (95% CI)		**10896**		**10769**	**100.0%**	**0.75 [0.65 , 0.88]**
Total events:	300		389			

Heterogeneity: Chi² = 7.64, df = 8 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.63 (P = 0.0003)
Test for subgroup differences: Not applicable



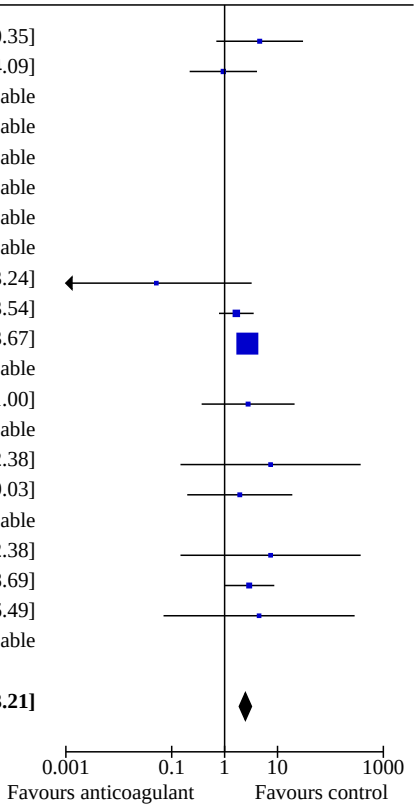
Analysis 1.6. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 6: Symptomatic intracranial haemorrhage during treatment period

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARGIS-1 2004	5	118	0	58	1.9%	4.60 [0.70 , 30.35]
ARTSS-2 2017	6	61	3	29	3.2%	0.95 [0.22 , 4.09]
CESG 1983	0	24	0	21		Not estimable
Chaudhary 2002	0	15	0	15		Not estimable
Dluha 2016	0	2	0	26		Not estimable
Dluha 2016	0	34	0	26		Not estimable
Duke 1983	0	35	0	30		Not estimable
Duke 1986	0	112	0	113		Not estimable
FISS 1995	0	207	1	105	0.4%	0.05 [0.00 , 3.24]
FISS-bis 1998	25	516	7	250	12.2%	1.67 [0.78 , 3.54]
IST 1997	120	9717	41	9718	72.1%	2.69 [1.97 , 3.67]
Liu 2020	0	30	0	30		Not estimable
Marshall 1960	3	26	1	25	1.7%	2.78 [0.37 , 21.00]
Pambianco 1995	0	64	0	67		Not estimable
Prins 1989	1	30	0	30	0.5%	7.39 [0.15 , 372.38]
Sandset 1990	2	52	1	51	1.3%	1.94 [0.20 , 19.03]
Sarma 2003	0	20	0	20		Not estimable
Tazaki 1992	1	69	0	69	0.5%	7.39 [0.15 , 372.38]
TOAST 1998	10	646	3	635	5.8%	2.91 [0.98 , 8.69]
Turpie 1987	1	50	0	25	0.4%	4.48 [0.07 , 286.49]
Vissinger 1995	0	20	0	30		Not estimable
Total (95% CI)		**11848**		**11373**	**100.0%**	**2.47 [1.90 , 3.21]**
Total events:	174		57			

Heterogeneity: Chi² = 7.58, df = 10 (P = 0.67); I² = 0%

Test for overall effect: Z = 6.73 (P < 0.00001)

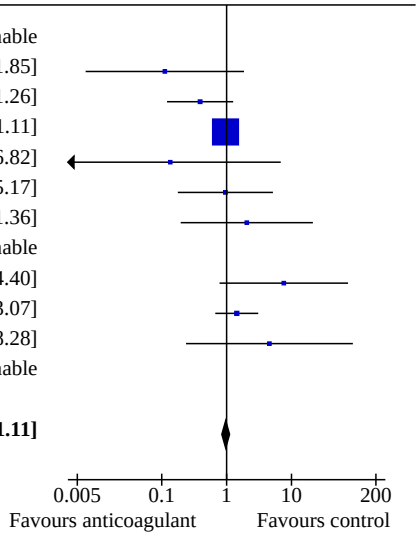
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 7: Any recurrent stroke or symptomatic intracranial haemorrhage during treatment period or follow-up (> 1 month)

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Cazzato 1989	0	28	0	29		Not estimable
CESG 1983	0	24	2	21	0.2%	0.11 [0.01 , 1.85]
FISS 1995	6	207	7	105	1.3%	0.39 [0.12 , 1.26]
IST 1997	396	9717	411	9718	93.5%	0.96 [0.84 , 1.11]
Liu 2020	0	30	1	30	0.1%	0.14 [0.00 , 6.82]
Marshall 1960	3	26	3	25	0.7%	0.96 [0.18 , 5.17]
NAT-COOP 1962	2	15	1	15	0.3%	2.05 [0.20 , 21.36]
Pambianco 1995	0	64	0	67		Not estimable
Tazaki 1992	3	69	0	69	0.4%	7.61 [0.78 , 74.40]
TOAST 1998	16	646	11	635	3.2%	1.43 [0.67 , 3.07]
Turpie 1987	2	50	0	25	0.2%	4.57 [0.24 , 88.28]
Vissinger 1995	0	20	0	30		Not estimable
Total (95% CI)		**10896**		**10769**	**100.0%**	**0.97 [0.84 , 1.11]**
Total events:	428		436			

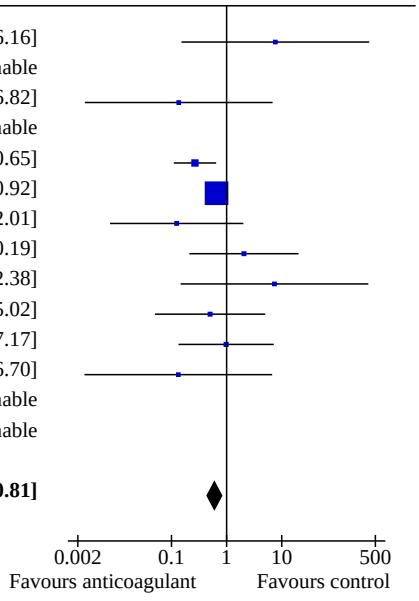
Heterogeneity: Chi² = 11.16, df = 8 (P = 0.19); I² = 28%
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 8: Symptomatic pulmonary embolism during treatment period

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Cazzato 1989	1	28	0	29	0.6%	7.66 [0.15 , 386.16]
CESG 1983	0	24	0	21		Not estimable
Elias 1990	0	15	1	15	0.6%	0.14 [0.00 , 6.82]
FISS 1995	0	207	0	105		Not estimable
FISS-bis 1998	9	516	14	250	11.7%	0.27 [0.11 , 0.65]
IST 1997	53	9716	81	9718	79.0%	0.66 [0.47 , 0.92]
Kwiecinski 1995	0	62	2	58	1.2%	0.12 [0.01 , 2.01]
Pambianco 1995	2	64	1	67	1.8%	2.06 [0.21 , 20.19]
Pince 1981	1	40	0	40	0.6%	7.39 [0.15 , 372.38]
Prins 1989	1	30	2	30	1.7%	0.50 [0.05 , 5.02]
Sandset 1990	2	52	2	51	2.3%	0.98 [0.13 , 7.17]
TOAST 1998	0	646	1	635	0.6%	0.13 [0.00 , 6.70]
Turpie 1987	0	50	0	25		Not estimable
Vissinger 1995	0	20	0	30		Not estimable
Total (95% CI)		**11470**		**11074**	**100.0%**	**0.60 [0.44 , 0.81]**
Total events:	69		104			

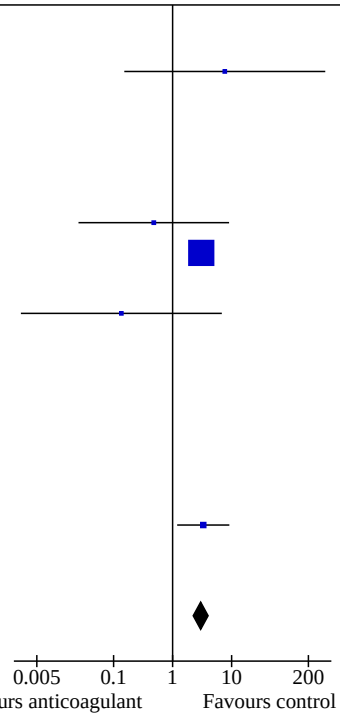
Heterogeneity: Chi² = 10.43, df = 9 (P = 0.32); I² = 14%
Test for overall effect: Z = 3.31 (P = 0.0009)
Test for subgroup differences: Not applicable



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

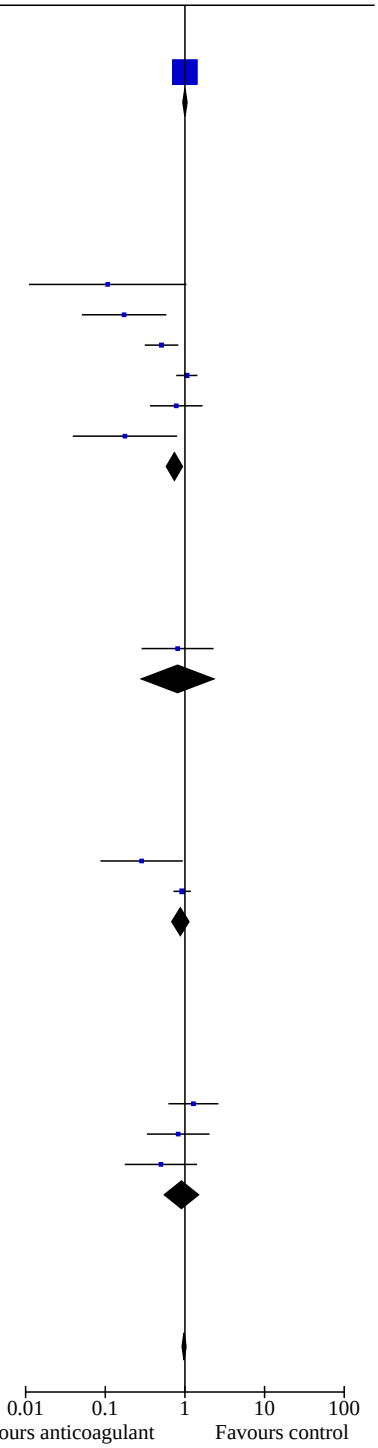
Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARGIS-1 2004	0	118	0	58		Not estimable
Cazzato 1989	1	28	0	29	0.5%	7.66 [0.15 , 386.16]
CESG 1983	0	24	0	21		Not estimable
Chaudhary 2002	0	15	0	15		Not estimable
Duke 1983	0	35	0	30		Not estimable
Elias 1990	0	15	0	15		Not estimable
FISS 1995	1	207	1	105	1.0%	0.48 [0.03 , 9.05]
IST 1997	129	9717	37	9718	89.8%	3.06 [2.25 , 4.15]
Marshall 1960	0	26	0	25		Not estimable
NAT-COOP 1962	0	15	1	15	0.5%	0.14 [0.00 , 6.82]
Pambianco 1995	0	64	0	67		Not estimable
Pince 1981	0	40	0	40		Not estimable
Prins 1989	0	30	0	30		Not estimable
Sandset 1990	0	52	0	51		Not estimable
Tazaki 1986	0	104	0	52		Not estimable
Tazaki 1992	0	69	0	69		Not estimable
TOAST 1998	12	646	3	635	8.1%	3.31 [1.20 , 9.15]
Turpie 1987	0	50	0	25		Not estimable
Total (95% CI)		**11255**		**11000**	**100.0%**	**2.99 [2.24 , 3.99]**
Total events:	143		42			

Heterogeneity: Chi² = 4.17, df = 4 (P = 0.38); I² = 4%
Test for overall effect: Z = 7.41 (P < 0.00001)
Test for subgroup differences: Not applicable



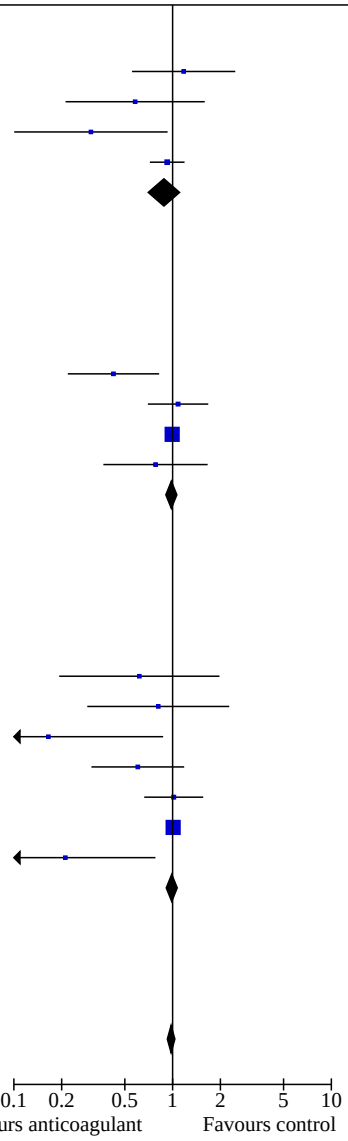
Analysis 1.10. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 10: Subgroup analysis by type of anticoagulant agent used: effect on death or dependency

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.10.1 Unfractionated heparin (subcutaneous) versus control						
IST 1997	6063	9717	6062	9718	86.8%	1.00 [0.94 , 1.06]
Subtotal (95% CI)		**9717**		**9718**	**86.8%**	**1.00 [0.94 , 1.06]**
Total events:	6063		6062			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
1.10.2 Low-molecular-weight heparin versus control						
Chaudhary 2002	1	15	6	15	0.2%	0.11 [0.01 , 1.04]
Dluha 2016	5	34	13	26	0.5%	0.17 [0.05 , 0.58]
FISS 1995	100	207	68	105	1.8%	0.51 [0.31 , 0.83]
FISS-bis 1998	300	516	142	250	3.1%	1.06 [0.78 , 1.43]
Kwiecinski 1995	19	62	21	58	0.6%	0.78 [0.36 , 1.67]
Sarma 2003	3	20	10	20	0.3%	0.18 [0.04 , 0.80]
Subtotal (95% CI)		**854**		**474**	**6.4%**	**0.74 [0.59 , 0.93]**
Total events:	428		260			
Heterogeneity: Chi² = 19.25, df = 5 (P = 0.002); I² = 74%						
Test for overall effect: Z = 2.58 (P = 0.010)						
1.10.3 Heparinoid (subcutaneous) versus control						
Cazzato 1989	13	28	15	29	0.3%	0.81 [0.29 , 2.29]
Subtotal (95% CI)		**28**		**29**	**0.3%**	**0.81 [0.29 , 2.29]**
Total events:	13		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
1.10.4 Heparinoid (intravenous) versus control						
Dluha 2016	6	27	13	26	0.4%	0.29 [0.09 , 0.94]
TOAST 1998	159	641	167	635	4.8%	0.92 [0.72 , 1.19]
Subtotal (95% CI)		**668**		**661**	**5.2%**	**0.88 [0.69 , 1.12]**
Total events:	165		180			
Heterogeneity: Chi² = 3.59, df = 1 (P = 0.06); I² = 72%						
Test for overall effect: Z = 1.06 (P = 0.29)						
1.10.5 Direct thrombin inhibitor versus control (intravenous)						
ARGIS-1 2004	43	83	21	46	0.5%	1.28 [0.62 , 2.64]
ARTSS-2 2017	35	61	18	29	0.4%	0.82 [0.33 , 2.03]
Liu 2020	10	30	15	30	0.4%	0.50 [0.18 , 1.42]
Subtotal (95% CI)		**174**		**105**	**1.3%**	**0.90 [0.55 , 1.48]**
Total events:	88		54			
Heterogeneity: Chi² = 2.17, df = 2 (P = 0.34); I² = 8%						
Test for overall effect: Z = 0.40 (P = 0.69)						
Total (95% CI)		**11441**		**10987**	**100.0%**	**0.98 [0.92 , 1.03]**
Total events:	6757		6571			
Heterogeneity: Chi² = 31.23, df = 12 (P = 0.002); I² = 62%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Test for subgroup differences: Chi² = 7.29, df = 4 (P = 0.12), I² = 45.2%						



Analysis 1.11. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 11: Subgroup analysis by anticoagulant dose: effect on death or dependency

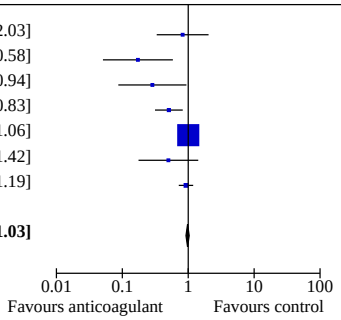
Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.11.1 Adjusted full-dose intravenous anticoagulant						
ARGIS-1 2004	58	86	30	47	0.5%	1.17 [0.56 , 2.48]
ARTSS-2 2017	15	31	18	29	0.3%	0.58 [0.21 , 1.59]
Dluha 2016	6	27	13	26	0.2%	0.31 [0.10 , 0.93]
TOAST 1998	159	641	167	635	4.7%	0.92 [0.72 , 1.19]
Subtotal (95% CI)		**785**		**737**	**5.8%**	**0.88 [0.70 , 1.11]**
Total events:	238		228			
Heterogeneity: Chi² = 4.84, df = 3 (P = 0.18); I² = 38%						
Test for overall effect: Z = 1.09 (P = 0.28)						
1.11.2 Medium fixed-dose anticoagulant						
FISS 1995	46	105	34	52	0.7%	0.42 [0.22 , 0.82]
FISS-bis 1998	145	245	71	124	1.6%	1.08 [0.70 , 1.68]
IST 1997	3022	4856	3031	4859	44.2%	0.99 [0.92 , 1.08]
Kwiecinski 1995	19	62	21	58	0.5%	0.78 [0.37 , 1.66]
Subtotal (95% CI)		**5268**		**5093**	**47.0%**	**0.98 [0.91 , 1.06]**
Total events:	3232		3157			
Heterogeneity: Chi² = 6.79, df = 3 (P = 0.08); I² = 56%						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.11.3 Low fixed-dose anticoagulant						
ARTSS-2 2017	21	30	23	29	0.2%	0.62 [0.19 , 1.97]
Cazzato 1989	13	28	15	29	0.3%	0.81 [0.29 , 2.27]
Chaudhary 2002	1	15	6	15	0.1%	0.17 [0.03 , 0.87]
FISS 1995	54	102	34	52	0.7%	0.60 [0.31 , 1.18]
FISS-bis 1998	155	271	71	125	1.6%	1.02 [0.66 , 1.56]
IST 1997	3041	4861	3031	4859	44.2%	1.01 [0.93 , 1.09]
Sarma 2003	3	20	10	20	0.2%	0.21 [0.06 , 0.78]
Subtotal (95% CI)		**5327**		**5129**	**47.2%**	**0.99 [0.91 , 1.07]**
Total events:	3288		3190			
Heterogeneity: Chi² = 12.87, df = 6 (P = 0.05); I² = 53%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Total (95% CI)		**11380**		**10959**	**100.0%**	**0.98 [0.93 , 1.03]**
Total events:	6758		6575			
Heterogeneity: Chi² = 25.37, df = 14 (P = 0.03); I² = 45%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Test for subgroup differences: Chi² = 0.87, df = 2 (P = 0.65), I² = 0%						

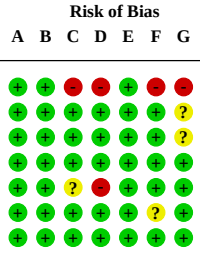


Analysis 1.12. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 12: Sensitivity analysis: dead or dependent at end of follow-up (if > 1 month) in trials with adequate concealment of treatment allocation

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARTSS-2 2017	35	61	18	29	0.4%	0.82 [0.33 , 2.03]
Dluha 2016	5	34	13	26	0.5%	0.17 [0.05 , 0.58]
Dluha 2016	6	27	13	26	0.4%	0.29 [0.09 , 0.94]
FISS 1995	100	207	68	105	1.9%	0.51 [0.31 , 0.83]
IST 1997	6063	9717	6062	9718	91.3%	1.00 [0.94 , 1.06]
Liu 2020	10	30	15	30	0.4%	0.50 [0.18 , 1.42]
TOAST 1998	159	641	167	635	5.1%	0.92 [0.72 , 1.19]
Total (95% CI)		**10717**		**10569**	**100.0%**	**0.98 [0.92 , 1.03]**
Total events:	6378		6356			

Heterogeneity: Chi² = 21.40, df = 6 (P = 0.002); I² = 72%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



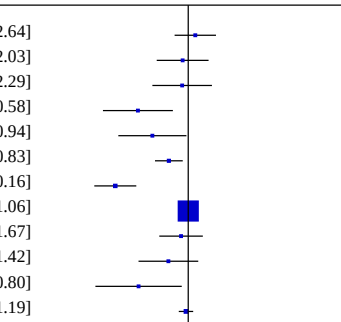


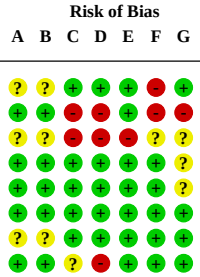
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.13. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 13: Sensitivity analysis: dead or dependent at end of follow-up (if > 1 month) for patients within 48 hours of stroke onset

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARGIS-1 2004	43	83	21	46	0.5%	1.28 [0.62 , 2.64]
ARTSS-2 2017	35	61	18	29	0.4%	0.82 [0.33 , 2.03]
Cazzato 1989	13	28	15	29	0.3%	0.81 [0.29 , 2.29]
Dluha 2016	5	34	13	26	0.5%	0.17 [0.05 , 0.58]
Dluha 2016	6	27	13	26	0.4%	0.29 [0.09 , 0.94]
FISS 1995	100	207	68	105	1.8%	0.51 [0.31 , 0.83]
FISS-bis 1998	300	516	142	150	3.5%	0.08 [0.04 , 0.16]
IST 1997	6063	9717	6062	9718	86.6%	1.00 [0.94 , 1.06]
Kwiecinski 1995	19	62	21	58	0.6%	0.78 [0.36 , 1.67]
Liu 2020	10	30	15	30	0.4%	0.50 [0.18 , 1.42]
Sarma 2003	3	20	10	20	0.3%	0.18 [0.04 , 0.80]
TOAST 1998	159	641	167	635	4.8%	0.92 [0.72 , 1.19]
Total (95% CI)		**11426**		**10872**	**100.0%**	**0.94 [0.89 , 1.00]**
Total events:	6756		6565			

Heterogeneity: Chi² = 73.09, df = 11 (P < 0.00001); I² = 85%
Test for overall effect: Z = 2.08 (P = 0.04)
Test for subgroup differences: Not applicable



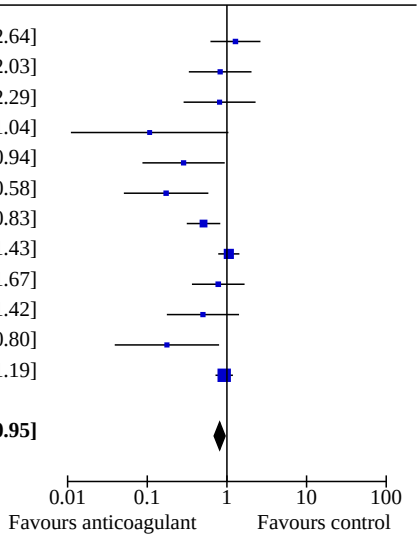


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.14. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 14: Sensitivity analysis: dead or dependent at end of follow-up (if > 1 month) excluding IST3 trial

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARGIS-1 2004	43	83	21	46	3.8%	1.28 [0.62 , 2.64]
ARTSS-2 2017	35	61	18	29	3.0%	0.82 [0.33 , 2.03]
Cazzato 1989	13	28	15	29	2.3%	0.81 [0.29 , 2.29]
Chaudhary 2002	1	15	6	15	1.6%	0.11 [0.01 , 1.04]
Dluha 2016	6	27	13	26	3.0%	0.29 [0.09 , 0.94]
Dluha 2016	5	34	13	26	3.6%	0.17 [0.05 , 0.58]
FISS 1995	100	207	68	105	13.5%	0.51 [0.31 , 0.83]
FISS-bis 1998	300	516	142	250	23.1%	1.06 [0.78 , 1.43]
Kwiecinski 1995	19	62	21	58	4.3%	0.78 [0.36 , 1.67]
Liu 2020	10	30	15	30	2.9%	0.50 [0.18 , 1.42]
Sarma 2003	3	20	10	20	2.5%	0.18 [0.04 , 0.80]
TOAST 1998	159	641	167	635	36.4%	0.92 [0.72 , 1.19]
Total (95% CI)		**1724**		**1269**	**100.0%**	**0.81 [0.69 , 0.95]**
Total events:	694		509			

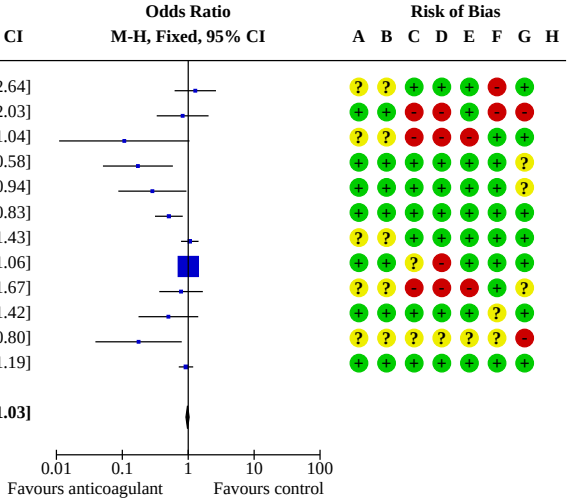
Heterogeneity: Chi² = 25.95, df = 11 (P = 0.007); I² = 58%
Test for overall effect: Z = 2.63 (P = 0.009)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 15: Sensitivity analysis: dead or dependent at end of follow-up (if > 1 month) excluding trial with assessment of primary outcome after only 1 month

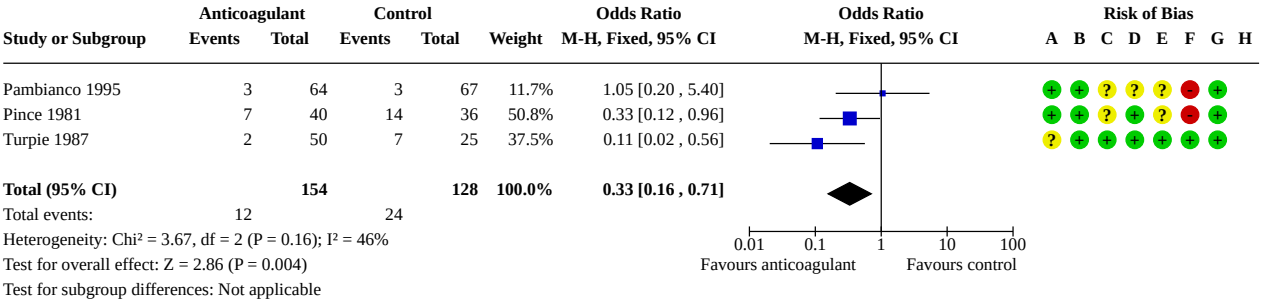
Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARGIS-1 2004	43	83	21	46	0.5%	1.28 [0.62 , 2.64]
ARTSS-2 2017	35	61	18	29	0.4%	0.82 [0.33 , 2.03]
Chaudhary 2002	1	15	6	15	0.2%	0.11 [0.01 , 1.04]
Dluha 2016	5	34	13	26	0.5%	0.17 [0.05 , 0.58]
Dluha 2016	6	27	13	26	0.4%	0.29 [0.09 , 0.94]
FISS 1995	100	207	68	105	1.8%	0.51 [0.31 , 0.83]
FISS-bis 1998	300	516	142	250	3.1%	1.06 [0.78 , 1.43]
IST 1997	6063	9717	6062	9718	87.1%	1.00 [0.94 , 1.06]
Kwiecinski 1995	19	62	21	58	0.6%	0.78 [0.36 , 1.67]
Liu 2020	10	30	15	30	0.4%	0.50 [0.18 , 1.42]
Sarma 2003	3	20	10	20	0.3%	0.18 [0.04 , 0.80]
TOAST 1998	159	641	167	635	4.8%	0.92 [0.72 , 1.19]
Total (95% CI)		**11413**		**10958**	**100.0%**	**0.98 [0.92 , 1.03]**
Total events:	6744		6556			

Heterogeneity: Chi² = 31.10, df = 11 (P = 0.001); I² = 65%
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable



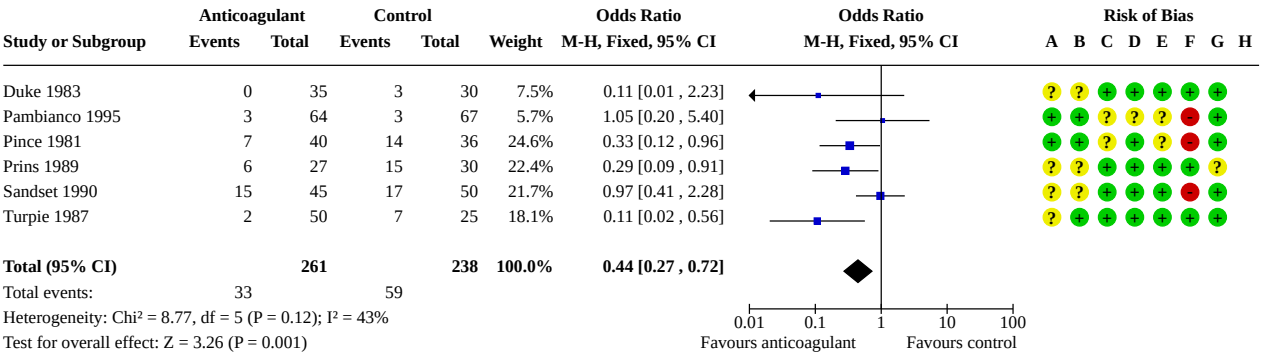
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.16. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 16: Sensitivity analysis: deep vein thrombosis during treatment period restricted to trials where concealment of allocation was secure



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.17. Comparison 1: Anticoagulant vs control in acute presumed ischaemic stroke, Outcome 17: Sensitivity analysis: deep vein thrombosis during treatment period restricted to trials where radiographic assessment was blinded



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

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, June 2007

Summary

This review of anticoagulant trials, including over 22,000 patients with acute ischaemic stroke, found no net benefit with the use of any anticoagulant. Consequently, the implications for practice and the implications for research are too timid. The implications for practice should say that anticoagulants should be contraindicated in patients with acute ischaemic stroke. The implications for research should say that further trials of anticoagulants in acute ischaemic 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
14 December 2021	Amended	Amendment to text of the plain language summary to improve clarity

HISTORY

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

Date	Event	Description
22 October 2021	New citation required but conclusions have not changed	Results and conclusions are unchanged
22 October 2021	New search has been performed	We have searched the literature for new relevant studies to April 2020. We have identified 4 new studies for inclusion. The review now includes 28 studies, involving 24,025 participants. We have reformatted and updated the text throughout.
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 in-

Date	Event	Description
		cluded 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 preparation of text for the 2015 update.

Xia Wang and Jie Yang rewrote the text of the 2020 update. Xia Wang, Menglu Ouyang, Jie Yang, and Ming Yang screened the new literature, extracted new data, and performed the analysis. Lili Song helped rewrite the text. Craig Anderson and Jie Yang supervised the analysis and writing of this report.

DECLARATIONS OF INTEREST

Xia Wang: *Grants and contracts:* investigator grant, post-doc fellowship (NHMRC National Heart Foundation Australia), "Those grants are for my salary support".

Menglu Ouyang: none known.

Jie Yang: *Grants and contracts:* funding support (National Natural Science Foundation of China), Grant No. 81870940.

Lili Song: none known.

Min Yang: none known.

Craig Anderson: *Grants and contracts:* research grants (Takeda China), approximately Aust$1m over 4 grants in as many studies. *Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events:* lecture fees and travel reimbursement (Takeda China), total approximately Aust$10k over 2 years. *Payment for a fellowship:* research fellowship (National Health and Medical Research Council (NHMRC) of Australia), "pays half my salary". *Work as a health professional*: "I am a consultant neurologist who manages patients with acute stroke" (Royal Prince Alfred Hospital, Sydney, Australia), clinical academic appointment.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

Activities of Daily Living; Anticoagulants [adverse effects]; *Brain Ischemia [drug therapy]; Heparin [adverse effects]; *Ischemic Stroke; *Stroke [drug therapy] [prevention & control]; Systematic Reviews as Topic

MeSH check words

Humans