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Sandercock PAG, Leong TS

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Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke.
Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD000119.
DOI: 10.1002/14651858.CD000119.pub4.

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[Intervention Review]

Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke

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Editorial group: Cochrane Stroke Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 4, 2017.

Citation: Sandercock PAG, Leong TS. Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No.: CD000119. DOI: 10.1002/14651858.CD000119.pub4.

ABSTRACT

Background

Low-molecular-weight heparins (LMWHs) and heparinoids are anticoagulants that may have more powerful antithrombotic effects than standard unfractionated heparin (UFH) but a lower risk of bleeding complications. This is an update of the original Cochrane Review of these agents, first published in 2001 and last updated in 2008.

Objectives

To determine whether antithrombotic therapy with LMWHs or heparinoids is associated with a reduction in the proportion of people who are dead or dependent for activities in daily living compared with UFH.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched February 2017), the Cochrane Central Register of Controlled Trials (CENTRAL: *the Cochrane Library* Issue 1, 2017), MEDLINE (1966 to February 2017), and Embase (1980 to February 2017). We also searched trials registers to February 2017: ClinicalTrials.gov, EU Clinical Trials Register, Stroke Trials Registry, ISRCTN Registry and the World Health Organization (WHO) International Clinical Trials Registry Platform.

Selection criteria

Unconfounded randomised trials comparing LMWH or heparinoids with standard UFH in people with acute ischaemic stroke, in which participants were recruited within 14 days of stroke onset.

Data collection and analysis

Two review authors independently chose studies for inclusion, assessed risk of bias and trial quality, extracted and analysed the data. Differences were resolved by discussion.

Main results

We included nine trials involving 3137 participants. We did not identify any new trials for inclusion in this updated review. None of the studies reported data on the primary outcome in sufficient detail to enable analysis for the review. Overall, there was a moderate risk of bias in the included studies. Compared with UFH, there was no evidence of an effect of LMWH or heparinoids on death from all causes during the treatment period (96/1616 allocated LMWH/heparinoid versus 78/1486 allocated UFH; odds ratio (OR) 1.06, 95% CI 0.78 to 1.47; 8 trials, 3102 participants, low quality evidence). LMWH or heparinoid were associated with a significant reduction in deep vein thrombosis (DVT) compared with UFH (OR 0.55, 95% CI 0.44 to 0.70, 7 trials, 2585 participants, low quality evidence). However, the number of the major clinical events such as pulmonary embolism (PE) and intracranial haemorrhage was too small to provide a reliable estimate of the effects.

Authors' conclusions

Treatment with a LMWH or heparinoid after acute ischaemic stroke appears to decrease the occurrence of DVT compared with standard UFH, but there are too few data to provide reliable information on their effects on other important outcomes, including functional outcome, death and intracranial haemorrhage.

PLAIN LANGUAGE SUMMARY

Which types of blood-thinning drugs (anticoagulants) are best to prevent blood clots in people soon after stroke?

Review question

This review aimed to find out which type of blood-thinning drug works best for preventing blood clots in people who have recently had a stroke due to blockage of an artery in the brain.

Background

Stroke is a common and disabling disease. Sudden blockage of an artery to the brain, often caused by a blood clot, is the cause of the most common type of stroke. This type is called an ischaemic stroke. Anticoagulants (blood-thinning drugs), are widely used in people with stroke. As stroke is a medical emergency, and medicines given in an emergency need to reach the bloodstream quickly, these are given by injection. Injectable anticoagulants that have been tested in stroke are unfractionated heparin (UFH), low-molecular-weight heparins (LMWH), and heparinoids. These agents may help clear blocked arteries, prevent re-blockage, and prevent clots forming in leg veins (deep vein thrombosis, DVT) after an ischaemic stroke and so might prevent fatal or disabling complications of stroke and improve the chance of a good recovery. However, they can also cause harmful bleeding complications that can offset any benefits.

Search date

The search was updated to February 2017.

Study characteristics

We looked for randomised controlled trials in people with recent onset of stroke symptoms that compared LMWH or heparinoids with UFH.

Key results

We found nine trials involving 3137 participants; overall these trials had a moderate risk of bias (this means that the results are likely to be less credible than if the risk of bias was low). No new trials were included in this updated review. None of the studies reported reliable information on disability or recovery after stroke. Compared with UFH, there was no evidence of an effect of LMWH or heparinoids on death from all causes during the treatment period (quality of the evidence was low). Although LMWH or heparinoid were associated with significantly fewer clots in leg veins (DVT) than UFH, the number of major events such as when a blood clot becomes lodged in an artery in the lung (pulmonary embolism) and bleeding inside the skull (intracranial haemorrhages) was too small to know whether the harms outweighed the benefits. For people with ischaemic stroke who need immediate treatment with anticoagulants, evidence from the included clinical trials did not provide reliable evidence on the balance of risk and benefit for each type of heparin. Additional large scale research would be needed to resolve this uncertainty.

Quality of the evidence

Overall, there was a moderate risk of bias in the included studies. Using GRADE criteria we found that evidence quality was low overall.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Low-molecular-weight heparins or heparinoids compared with unfractionated heparin for acute ischaemic stroke

Low-molecular-weight heparins (LMWH) or heparinoids compared with unfractionated heparin (UFH) for acute ischaemic stroke

Patient or population: acute ischaemic stroke
Setting: patients admitted to hospital with stroke of sufficient severity to cause immobility
Intervention: LMWH/heparinoids
Comparison: UFH

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with UFH	Risk with LMWH/heparinoids				
Death from all causes during treatment (range 6 days to 16 days)	Moderate risk population		OR 1.06 (0.78 to 1.46)	3102 (8 RCTs)	⊕⊕⊖⊖ LOW[1] [2]	
	90 per 1000[3]	95 per 1000 (72 to 126)				
	High risk population					
	131 per 1000[4]	138 per 1000 (105 to 180)				
Death from all causes during follow up (range 2 weeks to 12 weeks)	Moderate risk population		OR 0.98 (0.79 to 1.23)	3102 (8 RCTs)	⊕⊕⊖⊖ LOW[1] [2]	
	225 per 1000[3]	221 per 1000 (187 to 263)				
	High risk population					
	251 per 1000[4]	247 per 1000 (209 to 292)				
Deep vein thrombosis during treatment period (range 6 days to 16 days)	Moderate risk population		OR 0.55 (0.44 to 0.70)	2585 (7 RCTs)	⊕⊕⊖⊖ LOW[1] [5]	
	189 per 1000[6]	114 per 1000 (93 to 140)				
	High risk population					

	211 per 1000[4]	128 per 1000 (105 to 158)			
Pulmonary embolism during treatment period (range 6 days to 16 days)	Moderate		OR 0.57 (0.23 to 1.41)	1250 (6 RCTs)	⊕⊕⊝⊝ LOW[1 7]
	5 per 1000[3]	3 per 1000 (1 to 7)			
	High risk population				
	24 per 1000[4]	14 per 1000 (6 to 34)			
Symptomatic intracranial haemorrhage/haemorrhagic transformation of the cerebral infarct during treatment period (range 6 days to 16 days)[9]	Moderate risk population		OR 0.73 (0.35 to 1.54)	3102 (8 RCTs)	⊕⊕⊝⊝ LOW[1 8]
	12 per 1000[3]	9 per 1000 (4 to 18)			

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

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **RCT**: randomised controlled trial; **LWMH**: low-molecular-weight heparin; **UFH**: unfractionated heparin

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] There were unclear risk of selection bias in Hageluken 1992, Dumas 1994, Stiekema 1988, TRACE 2004, Turpie 1992 and Wong 2000. Hageluken 1992 and Stiekema 1988 were single blinded studies; PREVAIL 2007 was an open label study. Hence, making all these study high risk of performance and detection bias (downgraded 1 level).
[2] Small number of deaths were recorded throughout studies (downgraded 1 level).
[3] Calculated based on control event rate from IST 1997 where based on the inclusion criteria, it was interpreted that people are of average risk (hence, they are classified as 'moderate risk population') of developing complications such as deep vein thrombosis (DVT), pulmonary embolism (PE), cranial haemorrhages etc. that resulted in death or disability.
[4] Calculated based on control event rate from CLOTS3 2015 trial where based on the inclusion criteria, people are of high risk (hence they are classified as 'high risk population') of developing complications such as DVT, PE, cranial haemorrhages that resulted in death or disability.
[5] Methods of detection of detection of DVT were variable across the studies (downgraded 1 level).
[6] Calculated based on mean baseline risk from the studies of this Cochrane Review because IST 1997 did not include this outcome data.
[7] Small number of PEs across the studies.
[8] Small number of symptomatic intracranial haemorrhage across studies.
[9] High risk population not available as CLOTS3 2015 trial did not include this outcome data.

BACKGROUND

Low-molecular-weight heparins (LMWHs) and heparinoids are anticoagulants that may have more powerful antithrombotic effects than standard unfractionated heparin (UFH) but a lower risk of bleeding complications. This is an update of the Cochrane Review *Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke*, first published in 2001 (Counsell 2001) and last updated in 2008 (Sandercock 2008).

Description of the condition

Worldwide, stroke is one of the most common causes of death and disability in both developed and developing countries (Lozano 2012). Four-fifths of all strokes are caused by reduction in, or blockage of, blood flow in the artery supplying a particular part of brain; this type of stroke is called an ischaemic stroke (Warlow 2008). A common cause of ischaemic stroke is a blood clot that developed in the heart or large arteries travelling through the circulation to block a brain blood vessel (Caplan 2009).

Description of the intervention

Anticoagulants act on different components of the coagulation system to reduce fibrin and thrombus formation (Holbrook 2012). Some anticoagulants, such as Vitamin K antagonists, can only be given by mouth, have a slow onset of action, and so are not suitable for use as an emergency treatment in acute stroke where prompt onset of effect is needed and where difficulty swallowing from the stroke may preclude oral administration. The anticoagulant agents that have commonly been used in people with stroke that can be given parenterally and have a rapid onset of action are unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs) and heparinoids (Sandercock 2015). Standard UFH is a sulphated polysaccharide that affects the coagulation pathway by inhibition of Factor Xa and thrombin activity (Choay 1989; Cruickshank 1991). LMWHs are smaller molecules derived from heparin and act predominantly to inhibit Factor Xa (Cella 1986; Gordon 1990; Weitz 1997). Heparinoids are aminoglycans that inhibit thrombin activity via activation of the effect of heparin co-factor 2 (Shorr 2008). LMWHs and heparinoids have better bioavailability and longer half-life compared with UFH (Garcia 2012; Meuleman 1992).

How the intervention might work

In people with ischaemic stroke who arrive in hospital within the first few hours of onset, anticoagulants may be used as an emergency treatment to help dissolve the blood clot blocking the cerebral vessel, or to prevent new blood clots forming in arteries or veins. Early use of anticoagulants in acute ischaemic stroke might therefore have several beneficial effects: to reduce cerebral damage from the initial stroke, prevent early recurrent ischaemic stroke, and prevent venous thromboembolic events (VTEs) (IST 1997). VTEs include deep vein thrombosis (DVT, a blood clot lodging in a deep vein of the leg) and pulmonary embolism (PE, a blood clot lodging in an artery in the lungs). These actions of anticoagulants might reduce the chance of death from vascular causes, increase the chance of neurological recovery, and so improve the person's overall clinical outcome after acute ischaemic stroke (Sandercock 2015).

Why it is important to do this review

Randomised trials comparing UFH, LMWH, and heparinoids with placebo have not provided any convincing evidence that these agents improve survival or functional outcome of people with acute ischaemic stroke (IST 1997; Sandercock 2015; TOAST 1998). This is probably because any reductions in early recurrent ischaemic stroke or PE were offset by similar-sized increases in intra- and extracranial haemorrhages (bleeding inside and outside the brain). There was no difference in the overall clinical outcome, at final follow up as measured by the proportion of people dead or dependent at the end of follow-up (IST 1997; Sandercock 2015; TOAST 1998).

However, the Cochrane Review of the randomised trials comparing anticoagulant regimens with control in acute ischaemic stroke showed that anticoagulant therapy significantly reduced the odds of DVT by about 66%, from a rate of about 44% in those allocated to control, to 15% in those allocated to anticoagulants (Gubitz 2004; Sandercock 2015). There was also a significant 36% reduction in the odds of PE with anticoagulants. Hence, clinicians may still wish to consider the use of heparin in low dose for the prevention of DVT and life threatening PE.

The coagulation cascades are inhibited non-specifically at a number of different sites by standard UFH. It also inhibits platelet function (Choay 1989). These multiple blood thinning effects may increase the potential for UFH to cause haemorrhage (Gordon 1990), and so anticoagulant agents with more specific sites of action may be associated with lower risks of haemorrhage. Two such classes of agents are LMWHs and heparinoids. LMWHs and heparinoids have a more powerful antithrombotic effect than UFH and they also have a much longer half-life (period for which a drug actively affects the body) (Gordon 1990; Meuleman 1992). Although, from the described pharmacodynamics and pharmacokinetics, LMWHs and heparinoids should be safer to use in acute stroke than UFH, a systematic review of trials of LMWH with control suggested the greater antithrombotic efficacy was offset by greater bleeding risk (Bath 2000).

Previous reviews of anticoagulants versus control provided only indirect comparisons of the safety and efficacy of the different agents and such indirect comparisons are prone to bias (Gubitz 2004; Sandercock 1993). Only trials providing a direct randomised comparison of LMWHs or heparinoids with UFH will provide an unbiased assessment of the risk of haemorrhage, vascular death, and the effect on overall clinical outcome. Hence, a Cochrane Review of all the randomised trials directly comparing LMWHs or heparinoids with UFH to provide an unbiased assessment of the merits of each agent was first published in 2005 and updated in 2008. In our view, since high dose heparin is still occasionally used as a treatment for stroke (Chung 2016) and low-dose heparins are still used for prevention of DVT and PE in up to 40% of people with stroke in the USA (Amin 2013), an update was required to determine whether there were any new trials that may potentially change the conclusions of the previous review.

OBJECTIVES

- Primary: to determine whether antithrombotic therapy with low-molecular-weight heparins (LMWH) or heparinoids is associated with a reduction in the proportion of people who are

dead or dependent for activities in daily living compared with unfractionated heparin (UFH).

- Secondary: to determine whether, compared with UFH antithrombotic therapy with LMWHs or heparinoids is associated with:
  - a difference in deaths;
  - a lower incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) compared with UFH;
  - a reduction of the risk of early recurrent ischaemic strokes compared with UFH;
  - an increased risk of fatal or disabling intracranial or extracranial haemorrhage.

Note: the previous versions of this Cochrane Review did not specify a primary outcome, but sought to compare the effects of LMWH and heparinoids and UFH across a range of outcomes. When this update was planned we defined the primary objective and the primary outcome to be consistent with other Cochrane Stroke Reviews, since the proportion of people who are dead or dependent for activities in daily living provides a single outcome that captures the net longer-term effect on the person of the benefits and harms of this short-term treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included all unconfounded and truly randomised trials in this Cochrane Review. In these trials, the use of low-molecular-weight heparins (LMWH) or heparinoids in the acute phase of ischaemic stroke was compared with standard unfractionated heparin (UFH) as control. We did not include randomised trials in which the method of allocation to treatment or control group was not adequately concealed (e.g. allocation by alternation, date of birth, hospital number, day of the week, or open random number list). This is because foreknowledge of treatment allocation might lead to biased allocation (Odgaard-Jensen 2011) and hence to misleading estimates of treatment effect.

Types of participants

We excluded trials that randomised people more than 14 days after onset of the stroke and trials in people with only transient ischaemic attacks because this Cochrane Review was confined to early treatment of acute stroke. It was not essential for all people to have computed tomography (CT) scanning before entry to the trial (we were interested in people with confirmed or presumed ischaemic stroke), but we excluded trials which only included people with definite haemorrhagic stroke (stroke due to bleeding in the brain rather than blockage of an artery).

Types of interventions

Trials that compared a LMWH or heparinoid possessing anticoagulant activity with UFH were eligible. The UFH was administered either as a low dose subcutaneous regimen or a high dose intravenous one.

The heparinoids currently available included: Org 10172/danaparoid (Orgaran), dermatan sulphate, mesoglycan, and pentosan polysulphate. The LMWHs or heparinoids were administered either intravenously or subcutaneously. We identified all trials, irrespective of whether the purpose of therapy was to prevent deep vein thrombosis (DVT) and pulmonary embolism (PE), to reduce neurological disability, or to reduce the risk of early recurrent ischaemic stroke.

The LMWHs currently available included: Kabi 2165/dalteparin (Fragmin); CY 216/nadroparin (Fraxiparine); CY 222; PK 10169/enoxaparin (Clexane/Lovenox); LHN-1/tinzaparin (Logiparin/Innohep); OP 2123/parnaparin (Fluxum); certoparin (Sandoparin); reviparin (Clivarine); and Sandoz LMWH.

Types of outcome measures

We aimed to extract from each trial the number of people originally allocated to each treatment group, and, in each treatment group, the number of people with the following outcome events.

Primary outcomes

To be consistent with current methodological guidance from the Cochrane Stroke Group Editorial Board, we defined a primary outcome for this update of the review. In previous versions, we had defined 10 outcomes, and did not specify a single primary outcome. For this update, from the previous list of 10 outcomes, we chose 'the proportion of people who had died or needed help with daily activities at six months after randomisation' as the most clinically relevant of the 10 as the primary and we then classed the remaining nine as secondary outcomes.

Secondary outcomes

- Death from any cause during the scheduled treatment period.
- Death from any cause during the scheduled follow-up period.
- Death from vascular causes during the scheduled treatment and follow-up period. We defined vascular death (i.e. definitely or possibly vascular) as any death due to stroke (including complications of immobility resulting from the stroke e.g. pneumonia) or due to cardiac, haemorrhagic, embolic, or other vascular causes.
- Objective evidence of the occurrence of DVT detected by a systematically applied method (i.e. I125 fibrinogen scanning, doppler ultrasound or systematic X-ray contrast venography) in all surviving participants during the scheduled treatment period (the detection of DVT after the treatment period tended to be non-systematic and therefore potentially biased).
- Participants with at least one confirmed PE diagnosed during the scheduled follow-up period, or at autopsy.
- Participants with any intracranial haemorrhage or haemorrhagic transformation of the cerebral infarct confirmed by systematic CT or magnetic resonance (MR) scanning at the end of the treatment period, or by autopsy.
- Participants with symptomatic intracranial haemorrhage or haemorrhagic transformation of the cerebral infarct (dead brain tissue) confirmed by CT or MR scanning after clinical deterioration, or by autopsy.
- Participants with any major or minor extracranial haemorrhage. The definition of major haemorrhage was usually taken from the original article but if none was given we defined it as any bleed resulting in death, transfusion or operation.
- Participants with a recurrent stroke during the scheduled treatment period that was either definitely ischaemic (haemorrhage excluded on CT or MR scan or at autopsy) or in

which the pathology was unknown because no CT or MR or autopsy was performed.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We attempted to identify all relevant trials regardless of language or publication status, and arranged translation of relevant papers where necessary.

Electronic searches

With the assistance of the Managing Editor, we searched the Cochrane Stroke Group Trials Register (date last searched 6 February 2017). In addition, we searched the following bibliographic databases and trial registers.

- Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 1) in the Cochrane Library (searched February 2017, Appendix 1);
- MEDLINE in Ovid (searched February 2017, Appendix 2);
- Embase in Ovid (searched February 2017, Appendix 3);
- ClinicalTrials.gov (clinicaltrials.gov/, searched February 2017, Appendix 4);
- EU Clinical Trials Register (clinicaltrialsregister.eu/ctr-search/search, search February 2017, Appendix 4);
- Stroke Trials Registry (strokecenter.org/trials/, searched February 2017, Appendix 4);
- ISRCTN Registry (isrctn.com/; searched February 2017, Appendix 4) (previously Current Controlled Trials (www.controlled-trials.com, searched September 2015); and
- WHO International Clinical Trials Registry Platform (who.int/ictrp/en/, searched February 2017, Appendix 4).

Searching other resources

In an effort to identify further published, unpublished and ongoing trials, we screened the reference lists of all relevant trials.

For previous versions of this review, we had:

- contacted the following companies that market LMWHs or heparinoids: Alfa Wasserman (parnaparin and dermatan sulphate), Kabi (dalteparin), Knoll (reviparin), Leo (tinzaparin), Mediolanum (dermatan sulphate), Novo (tinzaparin), Organon (danaparoid), Rhone-Poulenc Rorer (enoxaparin), Sandoz (Sandoz LMWH), and Sanofi Winthrop (nadroparin and CY222); and
- consulted a comprehensive guide to pharmaceutical development in the stroke field (MEDSTRATEGY 1995).

Data collection and analysis

Two review authors (PS and TL), with the assistance of the Cochrane Stroke Group Information Specialist, performed the searches for this update. The same two review authors independently screened abstracts and titles, and excluded irrelevant studies. We retrieved and independently assessed the full articles of the remaining studies based on the inclusion and exclusion criteria. We resolved disagreements by discussion.

Selection of studies

Two review authors (PS and CC for the original review; PS and SS for second update; PS and TL for this update) independently selected trials to be included in the review. We resolved disagreements by discussion. Two review authors also assessed the methodological quality of each trial separately.

Data extraction and management

The two review authors (PS and TL) independently extracted and cross-checked the data. We extracted data such as the number of people with each outcome event, by allocated treatment group, irrespective of compliance, and whether or not the person was subsequently deemed ineligible or otherwise excluded from treatment or follow-up. This approach was applied to allow for an intention-to-treat (ITT) analysis. We sought data on whether or not CT or MR scanning was performed prior to randomisation. If any of the above data items were not available in the publications, we sought further information by correspondence with the trial authors. We checked to see whether there was evidence to suggest that previously excluded studies should be included and whether ongoing or studies awaiting assessment could be included, but further information was not available for any of these studies.

Assessment of risk of bias in included studies

For previous versions of this review, the authors did not use a scoring system to assess quality but only assessed risk of bias of included studies. In the previous version, the table of included studies gave details of the randomisation method, blinding, whether an ITT analysis was possible from the published data, and the number of people lost to follow-up. The only dimension of risk of bias that we graded was allocation concealment. However, for this update, we scored the key elements of risk of bias for each included study according to current Cochrane guidelines (Higgins 2011) and generated a risk of bias summary table.

Measures of treatment effect

Trials of each type of anticoagulant, (LMWHs or heparinoids) were compared to UFH to assess whether there was any difference between these classes of anticoagulants. We reported relative effects as odds ratios (OR, the ratio of the odds of an unfavourable outcome among people treated with either LMWHs or heparinoids versus UFH). We calculated the OR using the Peto fixed-effect method with its 95% confidence interval (CI).

Unit of analysis issues

All the studies included in this review were trials in which all the participants were randomised and followed up for a fixed and pre-defined period. All analyses were by ITT where possible.

Dealing with missing data

We contacted original investigators to ask for missing data whenever possible. When this was not possible, we calculated best- and worst-case scenarios: the best-case scenario would mean participants with missing data were alive and the worst-case scenario would mean participants with missing data were dead.

Assessment of heterogeneity

We tested heterogeneity between study results with the I^2 statistic which measures the percentage of the variability in effect estimates

attributable to heterogeneity (rather than sampling error). We considered a value greater than 50% as substantial heterogeneity.

Assessment of reporting biases

We produced funnel plots for two outcomes, death from all causes during treatment period and death from all causes during follow-up period, to assess the presence of publication bias.

Data synthesis

We used Review Manager 5 for analysis (RevMan 2014). Trials of each type of anticoagulant, namely LMWHs or heparinoids were compared to UFH to assess whether there was any difference between these classes of anticoagulants. We also assessed the effects of different doses of LMWHs or heparinoids against UFH (5000 IU 12-hourly), applying a test for trend, with due allowance for the fact that such indirect comparisons are prone to bias.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis of the type of anticoagulant agent used (either LMWHs or heparinoids versus UFH) and the dose of anticoagulant used.

Sensitivity analysis

We carried out sensitivity analyses to determine how sensitive results are to reasonable changes in the assumptions that are made. Furthermore, the potential impact of missing data on the findings of the review was addressed in the Results section (risk of bias, attrition bias). We did not perform a sensitivity analysis based on the frequency of CT or MR scanning at baseline as all studies scanned 100% of patients before entry.

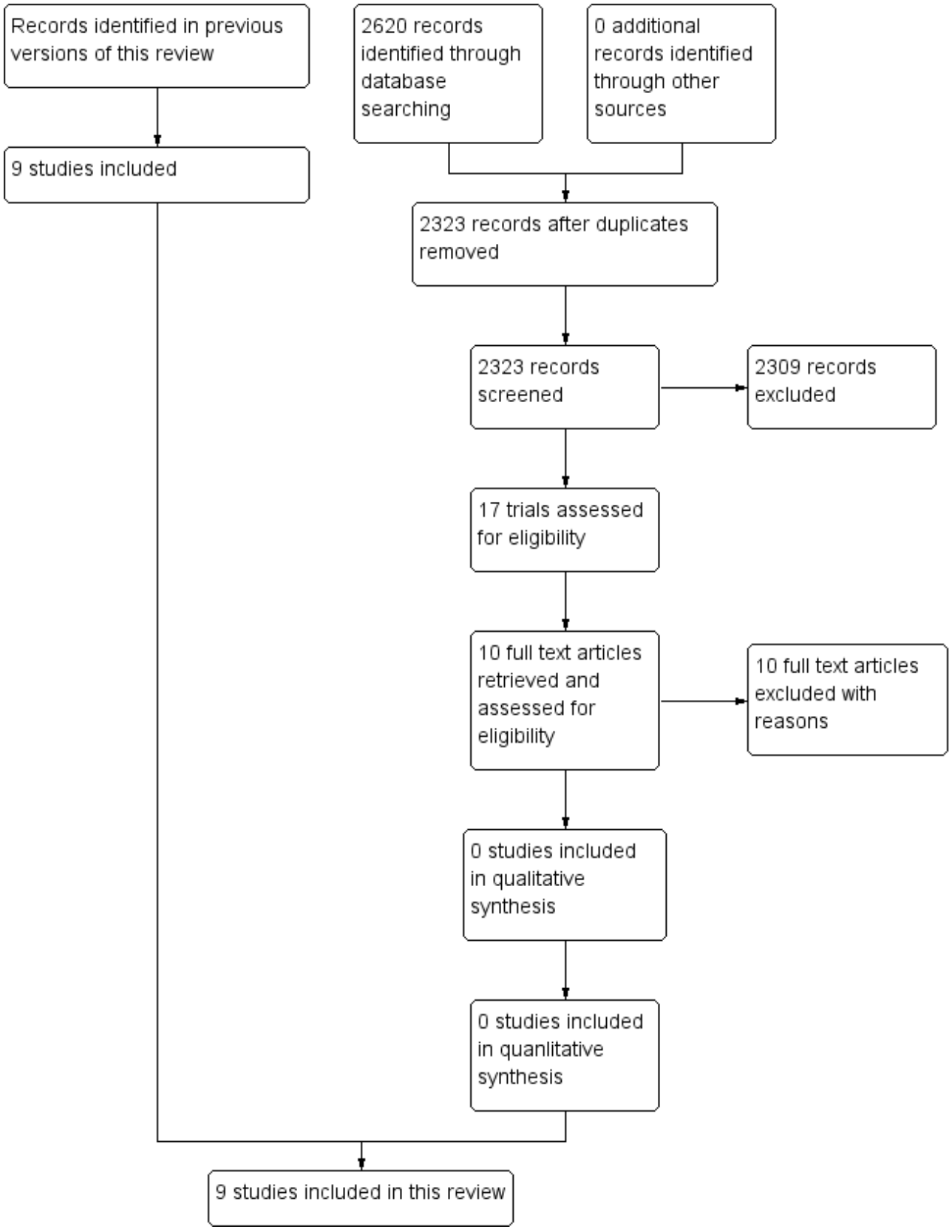
RESULTS

Description of studies

Results of the search

See the PRISMA flow diagram (Figure 1). After the removal of redundant records and previously included trials, we screened a total of 2620 records of titles and abstracts. We selected 17 apparently new trials and, of these, we obtained the full text reports for 10. We then excluded all of these studies after review, leaving no new trials for inclusion. Hence, from the last update, the number of included studies remained the same at nine trials. However, there was a sub-analysis of the PREVAIL 2007 trial which was published in 2009 that contained some additional relevant outcome data that was subsequently included in this updated review.

Figure 1. PRISMA flow diagram



Included studies

We included nine trials with a total number of 3137 participants (Dumas 1994; Hageluken 1992; Hillbom 1998; PREVAIL 2007; PROTECT 2006; Stiekema 1988; TRACE 2004; Turpie 1992; Wong 2000). Three of the trials have not yet been published in full (Hageluken 1992; Stiekema 1988; Wong 2000). The Characteristics of included studies table provides details of the included trials.

Most participants were enrolled within 72 hours of the stroke, except in two studies which recruited participants less than 24 hours after stroke onset (PROTECT 2006; TRACE 2004). The age of participants in the included trials ranged from 21 years to 91 years with a mean of 68 years. Most trials recruited slightly more males than females. Four trials compared danaparoid (a heparinoid) with unfractionated heparin (UFH) (Dumas 1994; Hageluken 1992; Stiekema 1988; Turpie 1992) and five compared low-molecular-weight heparin (LMWH) with UFH (Hillbom 1998; PREVAIL 2007; PROTECT 2006; TRACE 2004; Wong 2000). All trials administered treatment by the subcutaneous route, although in one trial, treatment began with a single intravenous loading dose of danaparoid (Stiekema 1988).

All the trials reported deaths, either during the treatment or follow-up periods. The scheduled period of treatment ranged from 6 days to 16 days. Duration of follow-up for all the trials was three months except for two trials, which followed up for 14 days (Stiekema 1988) and 28 days (Wong 2000). All the trials routinely performed computed tomography (CT) scanning in all participants before randomisation to exclude primary intracerebral haemorrhage as a cause of the stroke.

Attempts to contact the authors of a completed trial to gain additional information have been unsuccessful, so we were only able to include the outcome data on CT-confirmed haemorrhage from Wong 2000.

Excluded studies

We excluded 16 studies in this updated review. We had excluded eight trials from the previous review. In total, we excluded 24 studies for a variety of reasons. The Characteristics of excluded studies table provides summary details.

We excluded one study, comparing enoxaparin with UFH in 38 participants with stroke, because we had sought outcome data on the stroke subset of participants but these data were not provided (EMSG 1996). We excluded another two studies, comparing enoxaparin with UFH, because the stroke participants were not analysed separately and we were concerned that the participants in these two reports overlapped (Harenberg 1999; HESIM 1990). We also excluded studies where the target participants were not acute ischaemic stroke (Assadian 2008; NCT01763606; EXCLAIM 2010; Nikc Evic 2006).

We excluded a large number of studies because the intervention did not include unfractionated heparin (Dunatov 2008; EUROTOAST 1996; Geng 2004; MAGELLAN 2013; Mikulik 2006; Necioglu Orken 2009; Trencev 2008; Xing 2006) or LMWH (Trouillas 2008). One study was confounded because aspirin was part of its comparator (IRCT201109067495N1), and we excluded another study because the two treatment arms were confounded by the co-administration of different warfarin regimens (Feiz 2016). We excluded one trial because the treatment arms were confounded by differing background treatments (Heparinas 2013). One trial (Szirmai 1986) proved on review to have no control group, and we excluded another trial because no data were included in the report (McCarthy 1993).

Two trials published in China were only available as abstracts (Tan 2002; Wang 2012). We attempted to contact relevant authors as well as seek help from colleagues from China to obtain the full text articles but to no avail. A trial of CY 216 compared with UFH was stopped prematurely but remains unpublished and unavailable despite multiple contacts with the author (Moulin 1994). There are two apparently ongoing trials, but we have been unable to contact the authors to gain further information: one of enoxaparin versus UFH (Aventis 2002), and one of LMWH plus warfarin versus UFH plus warfarin (Young 2001).

While there are a large number of excluded studies, they all had small sample sizes, most were confounded in various ways and the inclusion of these studies would not be likely to reduce the random error or degree of bias in the estimates we have derived.

Risk of bias in included studies

Please refer to Figure 2 and Figure 3 for graphical representation of the risk of bias across all the nine studies. None of the included studies was assessed at low risk of bias in all categories, as each had some threats to validity. We considered some of the studies to have an unclear risk of bias due to the lack of details provided from the paper published. Overall, we judged there to be a moderate risk of bias, chiefly because of inadequate information about allocation concealment and risk of attrition bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

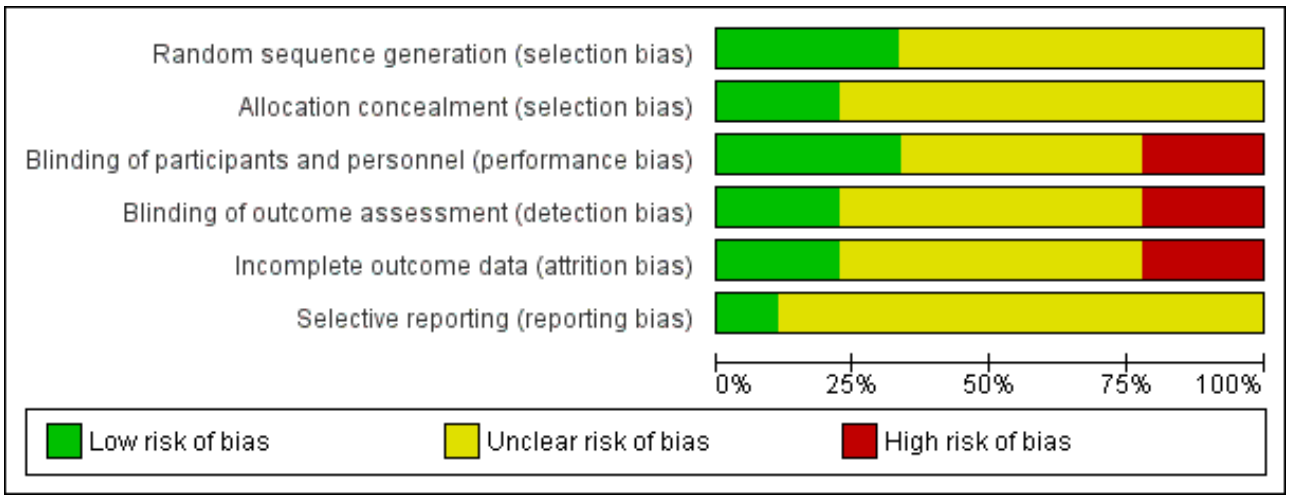
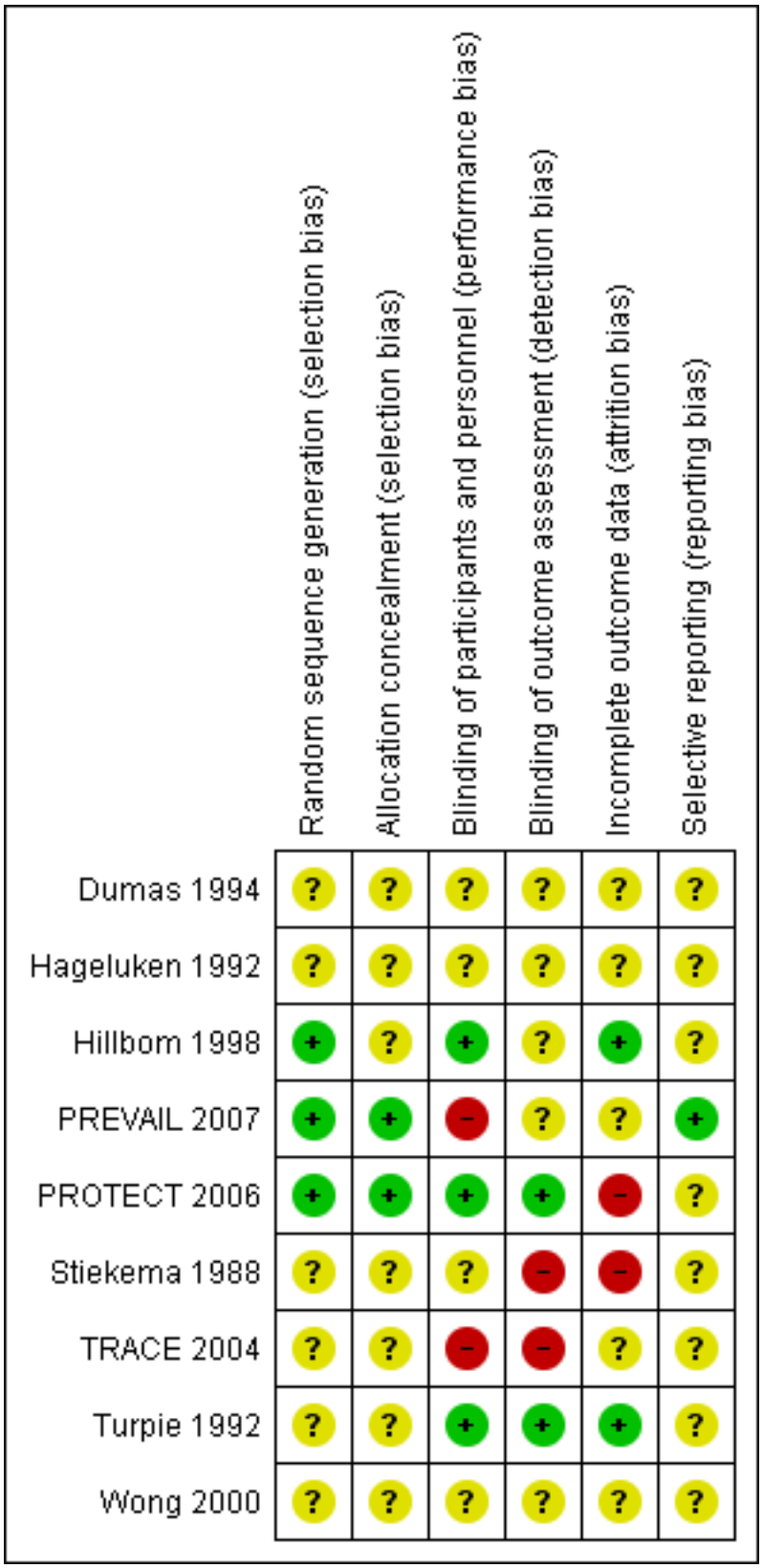


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The method of randomisation was described and considered adequate with low risk of bias in three out of nine of the included trials: Hillbom 1998 used a computer program (ACR/BIOM/STAT) to generate the randomisation sequence and a computer-generated randomisation list was used in PROTECT 2006. Hageluken 1992, Stiekema 1988, TRACE 2004, Turpie 1992 and Wong 2000 reported that the trial was randomised. Dumas 1994 used the sealed envelope method for randomisation. None of these six trials provided details on the method of random sequence generation.

Allocation concealment was adequate in PREVAIL 2007, which used a central randomisation system. Allocation concealment was unclear for six trials: in PROTECT 2006 the report stated only that "treatment allocation was kept strictly confidential and was available only to authorised persons", and in the other five, no details were given (Hageluken 1992; Stiekema 1988; TRACE 2004; Turpie 1992; Wong 2000). In Hageluken 1992 where there was a 3:1 treatment allocation to danaparoid and UFH respectively, there was a relative shortfall in the number of participants allocated to control with 118 allocated to danaparoid UFH and only 27 to control (and not about 40 as would be expected if randomisation had achieved a 3:1 ratio), which may have occurred by chance. However, there may be other explanations (such as deliberate or inadvertent subversion of the randomisation process, or unequal proportions of participants excluded after randomisation). Therefore, we performed analyses with this trial included and excluded, to assess its influence on the overall estimates of effect on the different outcomes.

Blinding

To reduce bias in detecting deep vein thrombosis (DVT), pulmonary embolism (PE), symptomatic intracranial haemorrhage and minor extracranial haemorrhages, adequate blinding is important. Four trials were double-blinded, where treatment allocation was not revealed to outcome assessors, participants and physicians (Dumas 1994; Hillbom 1998; PROTECT 2006; Turpie 1992). Hageluken 1992, Stiekema 1988, and Wong 2000 reported their assessors were single blinded. PREVAIL 2007 and TRACE 2004 did not use any form of blinding and were assessed at high risk of performance and detection bias.

Incomplete outcome data

Hillbom 1998 and Turpie 1992 stated explicitly that there were no losses to follow-up. PREVAIL 2007 and PROTECT 2006 published trial flow charts, which detailed the degree of losses to follow-up that was sufficient to be a significant source of attrition bias in both trials. The numbers of participants lost to follow-up was not stated in five trials (Dumas 1994; Hageluken 1992; Stiekema 1988; TRACE 2004; Wong 2000).

Selective reporting

Clinical trial registration details or study protocols were available for only one study (PREVAIL 2007). The primary publication for PREVAIL 2007 did not include numbers of participants who were dead or dependent at follow-up (a secondary paper in 2009 reported mean modified Rankin Scale: PREVAIL 2007). Data on recurrent strokes during the treatment period (up to 14 days) were reported in a subanalysis of PREVAIL 2007 published in 2009. Since these were secondary outcomes for the trial, we considered PREVAIL 2007 at low risk of reporting bias.

For the remainder of the included studies, it was unclear whether any of the older studies were free from reporting bias, largely because study protocols were not available. It is of note that only two provided information on functional outcomes: one on neurological deterioration within 10 days (Wong 2000); and the other on the Barthel index, a measure of functional independence (TRACE 2004). Neither PREVAIL 2007 nor TRACE 2004 provided numerical data. Given the overall quality of the older study reports, and their lack of detail on exactly what data were collected, one cannot rule out a degree of selective reporting of outcomes (in that era, internationally agreed reporting standards for clinical trials had not been published).

Other potential sources of bias

We sought evidence of publication bias but the number of studies was small (hence limiting the value of this analysis), and the funnel plots did not provide strong evidence of publication bias (Figure 4; Figure 5).

Figure 4. Funnel plot of comparison: 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, outcome: death from all causes during treatment period

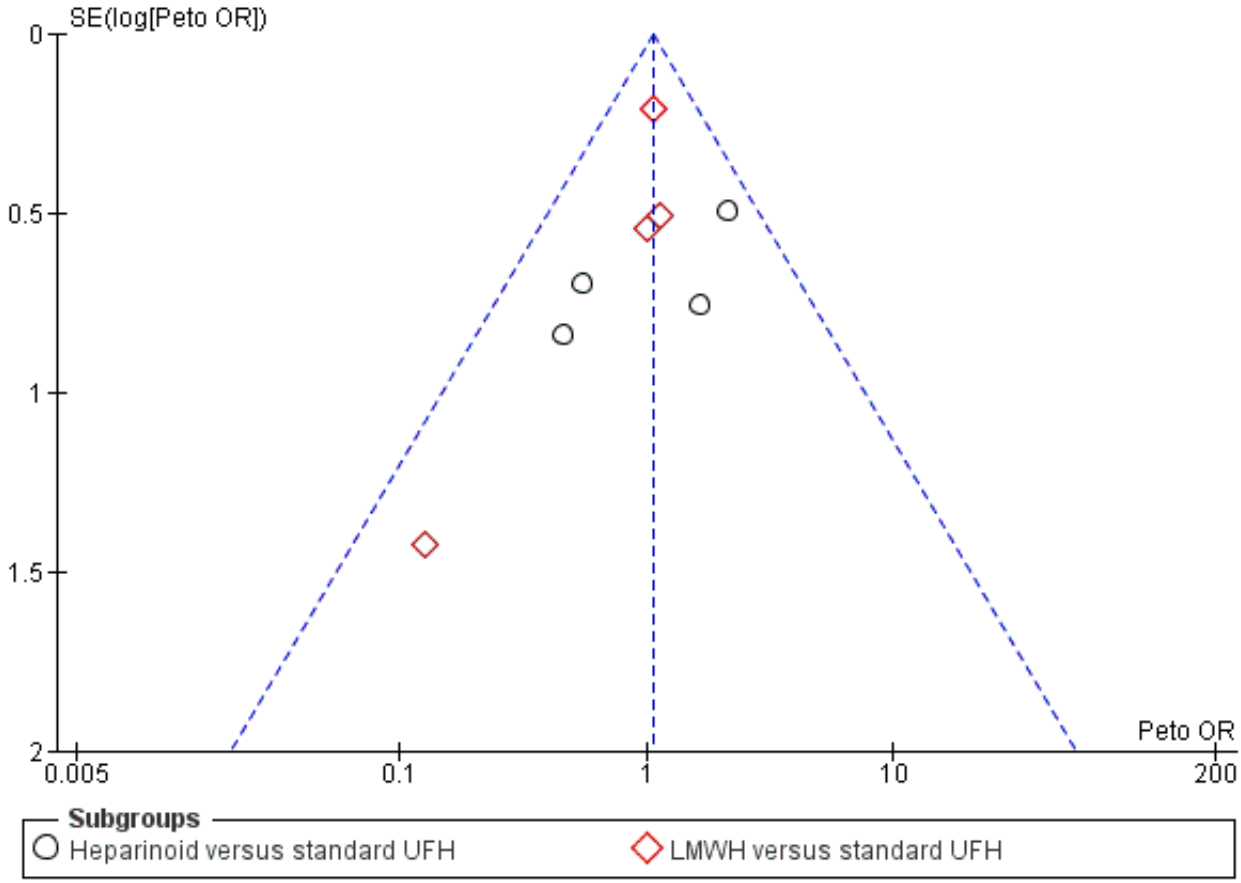
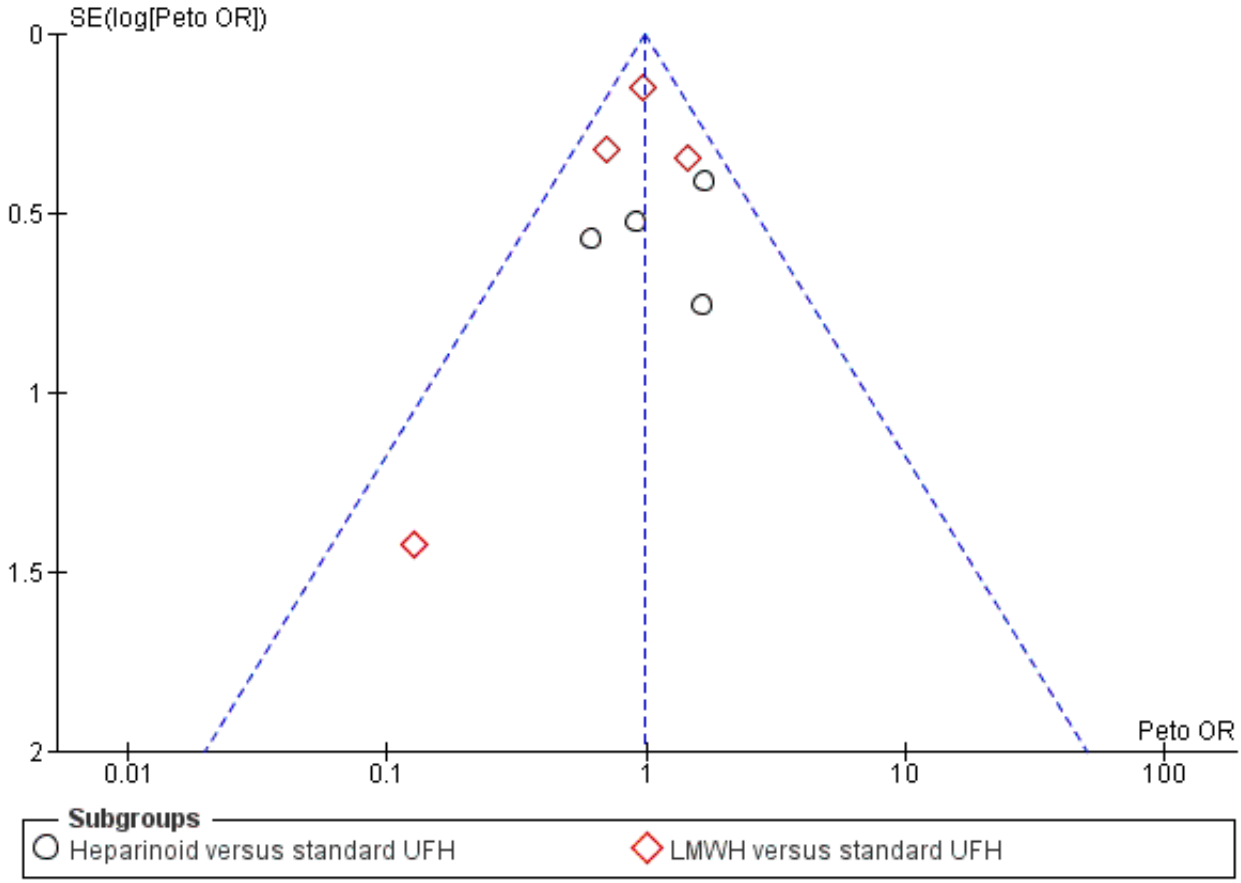


Figure 5. Funnel plot of comparison: 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, outcome: death from all causes during follow-up



Effects of interventions

See: **Summary of findings for the main comparison** Low-molecular-weight heparins or heparinoids compared with unfractionated heparin for acute ischaemic stroke

Outcome analysis 1.1: Dead or dependent at the end of follow-up

None of the trials reported this outcome in a form that enabled us to include them for this analysis.

Outcome analysis 1.2: Death from all causes during treatment period

During the anticoagulation period with LMWH, heparinoids, or UFH, an increased risk of death due to intracranial haemorrhage would only be apparent if most participants had autopsies or CT brain scan shortly before death. However, this was generally not the case, so reliable attribution of any deaths during the treatment period to intracranial haemorrhages was not possible. Intracranial haemorrhage carries an early case fatality of 50% or more, so analysis of deaths from all causes during the treatment period would be more sensitive to an excess of deaths related to intracranial haemorrhage than an analysis of all deaths during the whole of follow-up. Death data were available from eight trials (Dumas 1994; Hageluken 1992; Hillbom 1998; PREVAIL 2007; PROTECT 2006; Stiekema 1988; TRACE 2004; Turpie 1992) with 3102 participants (98.8% of the total participants included in the review). Overall, there was no significant difference in all cause death during the scheduled treatment period between LMWH or heparinoids and UFH (OR 1.06, 95% CI 0.78 to 1.46, low quality evidence; Analysis 1.2). There was no significant heterogeneity (I^2 = 0 %).

Outcome analysis 1.3: Death from all causes during follow-up

Data from eight trials with 3102 participants were available for this outcome. There was no significant difference between LMWH or heparinoid and UFH (OR 0.98, 95% CI 0.79 to 1.23, low quality evidence; Analysis 1.3). There was no significant heterogeneity (I^2 = 0 %) among the interventions. The confidence interval was compatible with substantial harm (an extra 2 deaths per 100 people treated) and substantial benefit (2 fewer deaths per 100 people treated). Any - even a small - excess of deaths associated with danaparoid or LMWH could clearly offset any benefits from reductions in DVT and PE.

Outcome analysis 1.4: Vascular death during follow-up

Significant and important beneficial or adverse effects on specific causes of death may be missed if crude analysis was undertaken only on deaths from all causes. Important effects of treatment on vascular deaths may be obscured if a large proportion of deaths were due to non-vascular causes (and hence very unlikely to be influenced by anticoagulant agents). Data on cause-specific

mortality in each treatment group with 1038 participants (33% of the total participants in the review) were available for this outcome. There was no significant difference in vascular death between those allocated danaparoid or LMWH versus those allocated UFH (OR 1.15, 95% CI 0.72 to 1.85, I^2 = 0%, low quality evidence; Analysis 1.4).

Outcome analysis 1.5: DVT during treatment period

Seven trials that included a total of 2585 participants (82.4% of the total number of participants included in the review) reported data on DVT detected systematically. Methods of detecting DVT were variable. Four trials used I^{125} fibrinogen scanning, two mostly used contrast venography, and one used Doppler ultrasound detecting only proximal leg DVT. Nevertheless, some participants either did not have the appropriate investigation or had an inadequate assessment of DVT. For instance, in Hillbom 1998 30 participants allocated enoxaparin and 34 allocated UFH did not have venography or had an inadequate examination; in Dumas 1994 four participants allocated UFH did not have valid I^{125} fibrinogen scans or venograms; in Hageluken 1992 16 participants allocated to danaparoid and eight participants allocated to UFH did not have valid DVT assessments; and in PREVAIL 2007 218 participants allocated enoxaparin and 209 allocated UFH had no or an inadequate assessment of DVT. These participants were retained in their original treatment groups for the main analysis, and we assumed that none had a DVT, except for PREVAIL 2007, where there were many excluded participants and so DVT was analysed in the per-protocol efficacy population.

The proportion of participants not undergoing venography was quite high in a number of studies. A modified worst-case scenario analysis was performed with the assumption that the excluded participants in the LMWH or heparinoid arm had a DVT rate that was equal to the highest rate in any arm in any included trial (31% in the Turpie 1992 UFH arm) and those excluded in the UFH arm had a DVT rate equal to the lowest rate in any arm (7% in the PROTECT 2006 LMWH arm). This method has been applied in other Cochrane Reviews (Macleod 2005; Sandercock 2003a).

As a whole, allocation to LMWH or heparinoid was associated with a significant reduction in DVT (OR 0.55, 95% CI 0.44 to 0.70, P < 0.00001, I^2 = 0%, low quality evidence; Analysis 1.5). However, the result was no longer statistically significant in the modified worst-case scenario analysis (OR 0.86, 95% CI 0.70 to 1.06). Both the heparinoid (OR 0.52, 95% CI 0.31 to 0.86, P = 0.01) and the LMWH (OR 0.56, 95% CI 0.44 to 0.73, P < 0.00001) regimens were associated with lower incidence of DVT compared with UFH.

Outcome analysis 1.6: PE during follow-up

Six trials, involving 1250 participants (39.8% of the total number of participants), presented data on symptomatic PE. However, not all surviving participants had pulmonary ventilation scans because confirmation of PE was not sought systematically. Furthermore, not all participants who died had autopsies, which could lead to bias in the results. In addition, there were too few participants with PE to generate substantial evidence on whether or not the observed trend in favour of LMWH or heparinoid was significant or happened merely by chance (OR 0.57, 95% CI 0.23 to 1.41, I^2 = 0%; Analysis 1.6). In the published report of Turpie 1992, no PEs were recorded, but unpublished data suggested a high possibility in one participant (who died but did not have an autopsy) in the UFH group. We excluded PREVAIL 2007 from our analyses because data were only available for the treatment period and not the scheduled follow-up period (PE occurring during the treatment in 1/666 enoxaparin versus 6/669 UFH participants, absolute risk difference –0.7%, 95% CI –1.5 to 0).

Outcome analysis 1.7: Any intracranial haemorrhage/ haemorrhagic transformation of the cerebral infarct during treatment period

Irresepctive of clinical deterioration, ideally an unbiased assessment of the effect of treatment on the occurrence of intracranial haemorrhage or haemorrhagic transformation of the infarct (HTI) would come from studies in which CT or MR scanning was performed systematically in all surviving participants at the beginning and end of the scheduled treatment period. However, the overall risk of intracranial haemorrhage may have been underestimated because it did not include those participants who may have died from an intracranial haemorrhage before a second scan could be performed and did not have an autopsy. The compromise of this scenario and the least biased and most fair assessment would be of the effect of treatment on the intracranial haemorrhage event or HTI detected by routine repeat CT scanning performed at the end of the scheduled treatment period in all survivors and by autopsy in all those who died during the treatment period (Sandercock 1993). However, none of the included studies undertook this as a pre-specified analysis.

All trials also reported intracranial haemorrhage associated with clinical deterioration (symptomatic HTI) but this analysis could lead to bias, particularly if the trial was not double-blind. In addition, the definition of deterioration varied between trials. 'Any HTI' was relatively uncommon (2.4% in all groups combined) and 'symptomatic HTI' was even more rare (0.9% in all groups combined). We may have underestimated the risk of any HTI somewhat because in Hillbom 1998 approximately 10% (20/212) of participants did not have a repeat CT scan and we assumed these participants did not have a haemorrhage. For this comparison (9 trials, 3137 participants) there was no significant difference in any HTI between LMWH or heparinoid and UFH (OR 0.75, 95% CI 0.46 to 1.23, P = 0.25, I^2 = 0%, low quality evidence; Analysis 1.7).

Outcome analysis 1.8: Symptomatic intracranial haemorrhage/haemorrhagic transformation of the infarct during treatment period

Data were available for eight trials (3102 participants). Overall, there was no significant difference in symptomatic HTI for LMWH or heparinoid versus UFH (OR 0.73, 95% CI 0.35 to 1.54, I^2 = 0%; Analysis 1.8). However, these analyses were based on very small numbers of events so the confidence intervals were very wide, implying that the available data were inadequate to provide reliable evidence on any possible excess risk of intracranial haemorrhage associated with LMWH or heparinoid compared with UFH.

Outcome analysis 1.9: Extracranial haemorrhage during treatment period

Seven trials (3012 participants; 96% of included participants) reported data on extracranial haemorrhage during the treatment period. Only 14 major extracranial haemorrhages occurred (0.5% of all participants); this very low absolute risk of serious bleeding is probably related to the fact that participants considered to be at high risk of bleeding were excluded from the trials. LMWH or danaparoid were associated with a substantially higher risk of

major extracranial bleeding than UFH (OR 3.79, 95% CI 1.30 to 11.06, I^2 = 0%; Analysis 1.9).

Information on minor haemorrhages is probably less reliable because it was less systematically reported and definitions varied; for example, some trials reported minor bruising at the injection site whilst others did not. Minor extracranial haemorrhages were common (6.5% of all participants) and were mainly related to skin haematomas (formed by blood clots, and giving rise to a swelling under the skin) at the injection sites, mild haematemesis (vomiting of blood) in participants with nasogastric tubes, or mild haematuria (blood in urine) in participants with urinary catheters. There was no difference in minor bleeds in those participants allocated to LMWH or danaparoid compared with UFH (OR 0.91, 95% CI 0.67 to 1.24, I^2 = 0%).

Outcome analysis 1.10: Effect of recurrent ischaemic stroke or recurrent stroke of unknown pathological type during treatment period

Two trials, TRACE 2004 and PREVAIL 2007, with 1839 participants, reported this outcome, which occurred in 8/923 participants allocated to LMWH or heparinoid versus 4/916 participants allocated to UFH; there was no evidence of a difference in this outcome between the two groups (OR 1.94, 95% CI 0.61 to 6.11, I^2 = 27%, low quality evidence; Analysis 1.10).

Indirect comparisons of different doses of heparinoid with standard heparin

Indirect comparisons suggested that 350 anti-Xa units daily of danaparoid may be less effective at preventing DVT than 5000 IU of UFH twice daily (although the data were limited; Analysis 1.11). Although there were trends towards greater benefit in terms of DVT prevention with larger doses of danaparoid and with twice daily compared with once daily administration, these were not significant and were based on very few data. The data on the safety of different doses of danaparoid with regard to haemorrhages were also extremely limited although there was the suggestion that higher doses or twice daily administration may produce more haemorrhages than UFH (Analysis 1.12).

Sensitivity analyses

There was no evidence of a significant difference in any outcome between danaparoid and LMWH. The inclusion or exclusion of three trials as a result of their potentially inadequate allocation concealment did not materially affect the overall conclusions (Hageluken 1992; TRACE 2004; Wong 2000).

Publication bias

We performed a funnel plot analysis to determine whether an important number of small negative trials were missed as a form of publication bias. We generated funnel plots for two outcomes: death from all causes during the treatment period (Figure 4), and death from all causes during follow-up period (Figure 5). These figures showed a degree of asymmetry, indicating possible publication bias, with under-reporting of studies favouring UFH. However, it should be interpreted with caution due to the small number of studies, making the power of the test too low to distinguish chance from real asymmetry (Higgins 2011).

DISCUSSION

It is not yet clear whether routine use of any anticoagulant treatment at all in acute stroke is beneficial (Sandercock 2015), and so it is perhaps premature to start comparing different anticoagulant regimens. In contrast, aspirin has been shown to be effective in improving neurological outcomes and preventing pulmonary embolism (PE) following ischaemic stroke and carries little risk of major haemorrhage (Sandercock 2014).

Summary of main results

Overall benefit of low-molecular-weight heparin (LMWH) or heparinoids versus unfractionated heparin (UFH) in acute ischaemic stroke

None of the included trials reported information on the primary outcome for this Cochrane Review update. Overall the included trials were at moderate risk of bias, and the quality of evidence for all outcomes assessed was low according to GRADE criteria. The analyses, which included only limited data on major clinical outcomes, suggested that, while LMWH or heparinoids may yield greater protection against deep vein thrombosis (DVT) than UFH, such benefits might be offset by an excess of intracranial haemorrhages and major extracranial haemorrhages, but the data on these potential risks in this update were inadequate. The numbers of deaths, intracranial haemorrhages, and major extracranial haemorrhages were small, and so the confidence intervals were wide and hence could not rule out significant harm from LMWH or heparinoids.

For example, in PREVAIL 2007, although the risk of venous thromboembolism (VTE) (symptomatic plus asymptomatic) was significantly lower among participants given LMWH, the study could not exclude a 69% increase in the risk of death up to day 14 and a 134% increase in the risk of intracranial haemorrhage with LMWH. This was because the event rates for these major clinical outcomes were low: PE and intracerebral haemorrhage occurred in 1% of participants respectively. It was challenging to conduct a trial large enough to assess the balance risk and benefit of the intervention with such low event rates.

Prevention of DVT and PE in acute ischaemic stroke by LMWH or heparinoids versus UFH

As a whole, allocation to LMWH or heparinoid was associated with a significant reduction in DVT but the result was no longer statistically significant in the modified worst-case scenario analysis. Many DVTs detected in stroke patients are clinically silent, and there is debate about the extent to which reductions in asymptomatic DVT correlate with reductions in clinically significant episodes of VTE (Lowe 2003). There were too few people with PE among the included trials to generate substantial evidence on whether or not the observed trend in favour of LMWH or heparinoid was merely by chance.

Risk of intra- and extracranial haemorrhage in acute ischaemic stroke with LMWH or heparinoids versus UFH

Although there was no significant difference in intracranial haemorrhage between LMWH or heparinoid and UFH during treatment periods, in participants allocated to LMWH or heparinoid versus UFH, there was a statistically significant increase in major extracranial haemorrhages. However, there were only 14 major

extracranial haemorrhages (0.5% of all participants). This very low absolute risk of serious bleeding was probably related to the fact that participants considered to be at high risk of bleeding were excluded from the trials. Information on minor haemorrhages should be interpreted cautiously because these events were systematically reported less frequently and definitions varied; for example, some trials reported minor bruising at the injection site but others did not. There was no difference in minor bleeds among participants allocated to LMWH or danaparoid compared with UFH.

Overall completeness and applicability of evidence

Most included trials were conducted more than 10 years ago, which may raise concerns about whether these results are still relevant for current clinical practice. The management of people with acute ischaemic stroke in the past two decades has changed, especially where acute stroke units have been established that provide better general care, early rehydration and active mobilisation which may reduce VTE frequency. On the other hand, greater use of intravenous thrombolysis may increase the haemorrhagic risks of anticoagulation. However, these changes in background clinical care may be expected to alter the absolute risks of various outcomes, but not greatly alter the estimates of relative effect of anticoagulation. It is unclear whether these data remain relevant in current clinical practice.

Quality of the evidence

Five of nine included trials did not specify methods of random sequence generation, and eight did not specify how allocation concealment was achieved, leading to assessment of unclear risk of selection bias. Most included trials did not provide sufficient information to enable assessment of selective reporting, hence risk of reporting bias was assessed as unclear (Figure 3). Overall, for each of the outcomes reported in our 'Summary of findings' table, the quality of evidence was graded as low. Furthermore, the largest trial, PREVAIL 2007 (N = 1762), was unblinded, which may have led to performance bias that could potentially affect review findings. The funnel plot analysis included too few studies to provide reliable evidence of, or reliably to exclude, publication bias.

This review does not reliably answer the question it set out to address: whether heparinoids or LMWHs are more effective, yet as safe as UFH to prevent neurological disability and VTE in people with acute ischaemic stroke. To provide guidance on which categories of people with ischaemic stroke may benefit from heparinoids or LMWHs, and more accurate and precise estimates of the risks of death and haemorrhage, much larger randomised controlled trials are required that compare danaparoid (or LMWHs) with UFH and with control in many thousands of participants. It is unlikely that any trial of this size could ever be performed.

Potential biases in the review process

Completeness of the searches: we are confident that the Cochrane Stroke Group Trials Register is an efficient and reliable way of identifying registered and ongoing trials relevant to this review. The extensive searches performed for the 2008 review and in 2015 for this update did not identify any major large-scale studies that were underway at the time of searching. The Cochrane Stroke Group Trials Register was searched again in July 2016 before this update was submitted. However, given the large number of apparently randomised stroke trials reported in scant detail in hard-to-access literature in China, it is possible that some may have been eligible for inclusion. The reports we have been able to obtain from China (Tan 2002; Wang 2012; Wong 2000) were only available as abstracts and none clearly met our inclusion criteria. At least one trial was closed but never reported data (Moulin 1994), and another three are thought to be ongoing trials but no details were available (Aventis 2002; Heparinas 2013; Young 2001). The changes to the protocol between the previous version and this update were minor and could not have introduced bias, since no data were available for our primary outcome.

Agreements and disagreements with other studies or reviews

A non-Cochrane review of LMWH versus UFH in people with ischaemic stroke supported the use of LMWH, due to the benefit of reducing venous thromboembolism (Shorr 2008). The study reported that there were no statistically significant increases in haemorrhage or death compared with UFH. However, a more recent and comprehensive review of heparin for DVT prophylaxis in medical patients found that in hospitalised medical patients (including those with stroke), heparin prophylaxis had no significant effect on mortality, may have reduced PE in medical patients and all patients combined, and led to more bleeding and major bleeding events, thus resulting in little or no net benefit (Lederle 2011).

What is new in this update?

For this update, the main searches were performed up to February 2017. We identified no new studies that met review inclusion criteria. We identified a report of a sub-analysis of the PREVAIL 2007 trial published in 2009 that contained limited additional outcome data which were subsequently included in this updated review. However, the overall results and conclusions remained the same as 2008 (Sandercock 2008). In previous versions of this review, outcomes were not divided into primary or secondary outcomes. In this updated review, the primary outcome was identified as the proportion dead or dependent in activities in daily living. We added more detailed assessment of risk of bias, funnel plots to assess for publication bias and a summary of findings table.

AUTHORS' CONCLUSIONS

Implications for practice

For clinicians who, despite the lack of evidence of overall benefit from routine anticoagulants in people with acute ischaemic stroke, still wish to use some form of anticoagulant regimen in selected people with acute ischaemic stroke:

- the criteria to identify those few people that might benefit from the unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or heparinoid regimens tested in these trials have not been defined;
- LMWH and heparinoids appear to be more effective at preventing deep venous thrombosis (DVT) - and possibly also pulmonary embolism (PE) - than UFH. However, their safety, compared with UFH, has not reliably been established in people with stroke.

Implications for research

It may well be that other antithrombotic agents, such as aspirin, will prove to be the antithrombotic agent with the most

favourable balance of risk and benefit for use in people with acute ischaemic stroke. Further very large-scale trials may be worthwhile comparing:

- aspirin alone with aspirin plus low-dose LMWH (or heparinoid) in individuals at particularly high risk of DVT and PE; and
- a more aggressive LMWH (or heparinoid) regimen with UFH and with aspirin only in certain categories of people, for example those with a cardiac source of emboli. These trials should measure disability and recurrent stroke as well as venous thromboembolism and major haemorrhages.

Given the lack of evidence for the routine use of any anticoagulant regimen in acute ischaemic stroke and the evidence in favour of using aspirin, further trials comparing only heparinoids or LMWH with UFH would be hard to justify.

ACKNOWLEDGEMENTS

We express appreciation to Hazel Fraser, Brenda Thomas, and Joshua Cheyne of the Cochrane Stroke Group for providing regular updates of newly identified trials and for help with trial searching. We also acknowledge Dr Carl Counsell and Dr Mei Chiun Tseng who contributed greatly for the previous version and updates of the review.

Ongoing trials

Any clinician who knows of additional trials that we have omitted please write to Professor Peter Sandercock.

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Hageluken 1992 *{unpublished data only}*

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Dumas 1994

Methods	R = sequentially numbered identical containers Double blind ITT Number lost to FU: not stated
Participants	Europe 76 men, 103 women, mean age 72 years 100% CT before entry Ischaemic stroke with leg paresis Less than 72 hours since stroke onset
Interventions	Rx: Org 10172 sc (1250 anti-Xa units 24-hourly) Control: heparin sc (5000 IU 12-hourly) Duration: 9 to 13 days
Outcomes	Death + cause of death DVT (systematic I^{125} scan with venography) PE (symptomatic) Intracranial haemorrhage (systematic CT) Extracranial haemorrhage
Notes	Ex: BP greater than 200/120, bleeding risk FU: 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not stated
Allocation concealment (selection bias)	Unclear risk	Sealed envelope, but no details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Treatment and control arms both involved 2 x daily injections. Manuscript states "patients, physicians and hospital staff were unaware of treatment allocation"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Treatment and control arms both involved 2 x daily injections. Manuscript states "patients, physicians and hospital staff were unaware of treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number lost to follow-up not stated
Selective reporting (reporting bias)	Unclear risk	Study protocol not available, study report does not give full details of data collected during follow-up

Hageluken 1992

Methods	R = sequentially numbered containers Single blind (assessor) ITT Number lost to FU: not stated
Participants	Europe 79 men, 66 women, mean age 69 years 100% CT before entry Ischaemic stroke with leg paresis Less than 72 hours since stroke onset
Interventions	Rx: Org 10172 sc (375 anti-Xa units 24-hourly); Org 10172 sc (750 anti-Xa units 24-hourly); Org 10172 sc (1250 anti-Xa units 24-hourly) Control: heparin sc (5000 IU 12-hourly) Duration: 9 to 11 days
Outcomes	Death + cause of death DVT (systematic I^{125} scan with venography) PE (symptomatic) Intracranial haemorrhage (systematic CT) Extracranial haemorrhage
Notes	Ex: BP greater than 200/120, bleeding risk FU: 3 months

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	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details provided
Selective reporting (reporting bias)	Unclear risk	Study protocol not available, study report does not give full details of data collected during follow-up

Hillbom 1998

Methods	R = sequentially numbered containers Double blind

Hillbom 1998 *(Continued)*

	ITT No loss to FU
Participants	Finland 127 men, 85 women, mean age 69 years 100% CT before entry Ischaemic stroke with leg paresis for more than 24 hours since stroke onset
Interventions	Rx: enoxaparin (40 mg once daily) Control: heparin sc (5000 IU 8-hourly) Duration: 10 ± 2 days or discharge if sooner
Outcomes	Death DVT (systematic venography) PE (symptomatic) Extracranial haemorrhage Intracranial haemorrhage (systematic CT)
Notes	Ex: specified by protocol - includes bleeding risk; GCS < 9; pre-existing DVT FU: 3 months Sponsoring pharmaceutical company stopped before planned sample size of 400 people recruited, because of very slow recruitment rate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedule had a block size of 4 and was generated by computer programme AC/BIOM/STAT
Allocation concealment (selection bias)	Unclear risk	Method for the participating doctor to obtain the treatment allocation not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Experimental and control treatments supplied in prefilled syringes of identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Steps to blind assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Manuscript states no patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Study protocol not available, study report does not give full details of data collected during follow-up

PREVAIL 2007

Methods	R = blocked and stratified randomisation, telephone to central randomisation system Study treatment was not blinded ITT Follow up: not available for 32 (15 Rx, 17 control) either by withdrawal of consent or loss to FU
Participants	International

PREVAIL 2007 *(Continued)*

	994 men, 768 women, mean age 66 years 100% CT or MRI before entry Ischaemic stroke and unable to walk unassisted < 48 hours since stroke onset NIHSS score 2 or more
Interventions	Rx: enoxaparin 40 mg sc once daily Control: heparin sc (5000 IU 12-hourly) Duration: 10 days (range 6 to 14)
Outcomes	Death DVT (systematic venography or ultrasound if venography not possible) PE (symptomatic) Extracranial haemorrhage Intracranial haemorrhage (systematic CT) Modified Rankin Scale
Notes	Ex: specified by protocol FU: 90 days Sponsored by Sanofi-Aventis (Paris, France)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sponsor generated the randomisation schedule in permuted blocks of 4, stratified by baseline stroke severity that was implemented centrally by an independent interactive voice-response system
Allocation concealment (selection bias)	Low risk	The randomisation schedule was implemented centrally by an independent interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not blinded, but all major outcome events were reviewed blind to treatment allocation by an adjudication committee
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Primary outcome data not available for 32 participants, number with missing modified Rankin Scale status not stated
Selective reporting (reporting bias)	Low risk	Trial registered NCT00077805, protocol-specified outcomes all reported

PROTECT 2006

Methods	R = computer-generated randomisation list Double-blind ITT Losses to follow up: 67 (34 Rx, 33 control)
Participants	European Union 313 men, 232 women, 18 to 85 years, mean age 67 years

PROTECT 2006 *(Continued)*

	100% CT before entry Ischaemic stroke with leg paresis Less than 24 hours since stroke onset NIHSS score 4 to 30
Interventions	Rx: certoparin sc (3000 U once daily) plus 2 injections of placebo Control: heparin sc (5000 IU 8-hourly) Duration: 12 to 16 days
Outcomes	Death related to DVT Proximal leg DVT (ultrasound) PE (symptomatic) Extracranial haemorrhage Intracranial haemorrhage (systematic CT)
Notes	Ex: specified by protocol - includes bleeding risk, body weight < 55 kg FU: 3 months Sponsored by Novartis (Nürnberg, Germany)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generated by computer
Allocation concealment (selection bias)	Low risk	Manuscript states "Treatment allocation kept strictly confidential and available only to authorised persons"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Experimental and control treatments identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Experimental and control treatments identical in appearance
Incomplete outcome data (attrition bias) All outcomes	High risk	64 (10%) participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Study protocol not available, study report does not give full details of data collected during follow-up

Stiekema 1988

Methods	R = sequentially numbered containers Single blind (assessor) Loss to follow-up not stated
Participants	Europe 43 men, 39 women, 21 to 91 years 100% CT before entry Ischaemic stroke with leg paresis Less than 72 hours since stroke

Stiekema 1988 *(Continued)*

Interventions	Rx: loading dose 1000 anti-Xa units iv, then Org 10172 sc (1250 anti-Xa units 12-hourly) or Org 10172 sc (750 anti-Xa units 12-hourly) Control: heparin sc (5000 IU 12-hourly) Duration: 10 days
Outcomes	Death + cause of death DVT (systematic I^{125} scan with venography) PE (symptomatic) Intracranial haemorrhage (systematic CT) Extracranial haemorrhage
Notes	Ex: BP > 200/120, bleeding risk FU: 14 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	Method of allocation concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Report to company describes this as an open trial, published abstract states double blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up not stated
Selective reporting (reporting bias)	Unclear risk	Study protocol not available, study report does not give full details of data collected during follow-up

TRACE 2004

Methods	R = not described Unblinded ITT Losses to follow up: not stated
Participants	Germany Caucasian, 57 men, 33 women, mean age 68 years 100% CT or MRI before entry Ischaemic stroke less than 24 hours since stroke onset
Interventions	Rx: enoxaparin 1 mg/kg sc twice daily (100 Anti-Xa units 12-hourly) Control: heparin iv (initial bolus of 80 IU/kg, followed by 18 IU/kg/h) Duration: 8 ± 2 days

TRACE 2004 *(Continued)*

Outcomes	Death Reduction in microembolic signals compared with baseline on day 2 and 5 (TCD verified) Cerebral ischaemic events, systemic embolic events, and bleeding complications Barthel Index
Notes	Ex: specified by protocol - includes bleeding risk, severe organic cerebral disease FU: 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	Study protocol not available, study report does not give full details of data collected during follow-up

Turpie 1992

Methods	R = sequentially numbered identical containers Double blind ITT No loss to FU
Participants	Canada 38 men, 49 women, mean age 72 years 100% CT before entry Non-embolic ischaemic stroke with leg paresis Les than 7 days since stroke onset
Interventions	Rx: Org 10172 sc (750 anti-Xa units 12-hourly) Control: heparin sc (5000 IU 12-hourly) Duration: 14 days
Outcomes	Death DVT (systematic I^{125} scan + plethysmography with venography) PE (symptomatic) Intracranial haemorrhage (systematic CT)

Turpie 1992 *(Continued)*

Notes	Ex: bleeding risk; pre-existing DVT FU: 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not stated
Allocation concealment (selection bias)	Unclear risk	Method for concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participamts, trial nurses, and physicians were all unaware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participamts, trial nurses, and physicians were all unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Study protocol not available, study report does not give full details of data collected during follow-up

Wong 2000

Methods	R = not stated Single blind (CT scans only) Loss to follow-up not stated
Participants	Taiwan 35 participants 2 groups had similar baseline characteristics 100% CT before entry Increase in severity or number of neurological symptoms less than 48 hours since stroke onset GCS decrease more than 2 points, limb weakness, onset of new neurological symptoms
Interventions	Rx: unspecified LMWH sc (0.4 mL 4100 anti-Xa IU twice daily) Control: heparin (5000 IU bolus, then 15,000 IU/day for 24 hours, then dose adjusted to maintain APTT ratio at 1.5 to 2) Duration: 10 days
Outcomes	Haemorrhagic transformation (systematic CT on day 10 or symptomatic before day 10) Barthel Index
Notes	Ex: progression due to brain oedema or intracranial haemorrhage FU: 28 days

Risk of bias

Wong 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	Study protocol not available, study report does not give full details of data collected during follow-up

APTT: activated partial thromboplastin time
BP: blood pressure
CT: computerised tomography
DVT: deep venous thrombosis
Ex: exclusion criteria
FU: follow up
GCS: Glasgow coma scale
ITT: intention-to-treat
iv: intravenously
LMWH: low-molecular-weight heparin
MRI: magnetic resonance imaging
mRS: ???
NIHSS: National Institutes of Health stroke Scale
PE: pulmonary embolism
R: randomisation method
Rx: treatment
sc: subcutaneously
TCD: transcranial doppler

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

Study	Reason for exclusion
Assadian 2008	Target participants were not people with acute ischaemic stroke
Dunatov 2008	Intervention did not include unfractionated heparin
EMSG 1996	Enoxaparin 20 mg subcutaneously once daily versus standard unfractionated heparin 5000 IU subcutaneously twice daily for 10 days in immobile people (38 strokes) Data on subset of participants with stroke are still awaited from sponsor
EUROTOAST 1996	Comparison of different doses of heparinoid, no UFH group

Study	Reason for exclusion
EXCLAIM 2010	Target participants were not people with acute ischaemic stroke
Feiz 2016	2 treatment groups confounded by co-administration of different warfarin regimens
Geng 2004	Intervention did not include UFH
Harenberg 1999	Enoxaparin versus heparin for prophylaxis of thromboembolic events in people with medical conditions Data have not been reported separately for people with stroke alone
Heparinas 2013	Ongoing trial of heparin versus nadroparin versus placebo. Complex confounded regimens
HESIM 1990	About 150 (19%) participants had neurological disease Data have not been reported separately for people with stroke alone Some data may be the same as those reported in Harenberg 1999
IRCT201109067495N1	Comparison of LMWH with aspirin instead of UFH
MAGELLAN 2013	Intervention did not include UFH
McCarthy 1993	Data have not been reported
Mikulik 2006	Intervention did not include UFH
Moulin 1994	Enoxaparin/CY216 versus standard UFH The trial was closed prematurely due to funding constraints Data have not been reported
NCT01763606	Target participants were not people with acute ischaemic stroke
Necioglu Orken 2009	Intervention did not include UFH
Nikc Evic 2006	Not acute stroke, method of treatment allocation not random
Szirmai 1986	Uncontrolled study
Tan 2002	Published in China and only available as an abstract. Attempted to contact authors as well as seek help from colleagues from China to obtain the full text article but to no avail
Trencev 2008	Intervention did not include UFH
Trouillas 2008	Intervention did not include LMWH
Wang 2012	Published in China and only available as an abstract. Attempted to contact authors as well as seek help from colleagues from China to obtain the full text article but to no avail
Xing 2006	Intervention did not include UFH

LMWH: low-molecular-weight heparin
UFH: unfractionated heparin

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

Aventis 2002

Trial name or title	An open-label, randomised, parallel group, multicentre study to evaluate the efficacy and safety of enoxaparin versus unfractionated heparin in the prevention of venous thromboembolism in people following acute ischaemic stroke
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	Ms S Wellington, Senior Clinical Project Leader, Aventis Pharma, Aventis House, 50 Kings Hill Avenue, Kings Hill, West Malling, Kent, UK
Notes	

Young 2001

Trial name or title	Low-molecular-weight heparin (enoxaparin) in anticoagulation transition to oral warfarin in ischaemic cerebral vascular accident or transient ischaemic attack
Methods	
Participants	Acute ischaemic stroke
Interventions	Enoxaparin sc + oral warfarin versus UFH sc + oral warfarin
Outcomes	
Starting date	
Contact information	Dr WD Young, North Mississippi Medical Centre, 830 S Gloster Street, Tupelo MS 38801, USA
Notes	

sc: subcutaneously
UFH: unfractionated heparin

DATA AND ANALYSES

Comparison 1. LMWH/heparinoid versus standard UFH in acute ischaemic stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dead or dependent at the end of follow-up	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

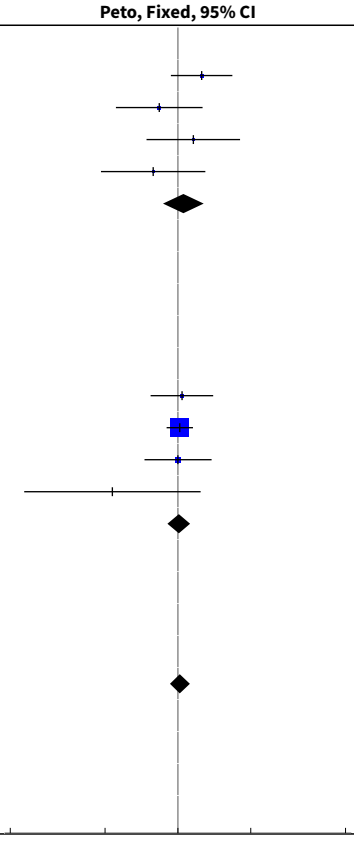
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Death from all causes during treatment period	8	3102	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.78, 1.46]
2.1 Heparinoid versus standard UFH	4	493	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.62, 2.26]
2.2 LMWH versus standard UFH	4	2609	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.72, 1.47]
3 Death from all causes during follow-up	8	3102	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.79, 1.23]
3.1 Heparinoid versus standard UFH	4	493	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.69, 1.94]
3.2 LMWH versus standard UFH	4	2609	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.74, 1.21]
4 Vascular death during follow-up	5	1038	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.72, 1.85]
4.1 Heparinoid versus standard UFH	4	493	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.68, 1.94]
4.2 LMWH versus standard UFH	1	545	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.39, 3.53]
5 Deep venous thrombosis during treatment period	7	2585	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.44, 0.70]
5.1 Heparinoid versus standard UFH	4	493	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.31, 0.86]
5.2 LMWH versus standard UFH	3	2092	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.44, 0.73]
6 Pulmonary embolism during follow-up	6	1250	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.57 [0.23, 1.41]
6.1 Heparinoid versus standard UFH	4	493	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.18, 2.21]
6.2 LMWH versus standard UFH	2	757	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.13, 1.90]
7 Any intracranial haemorrhage/haemorrhagic transformation of the cerebral infarct during treatment period	9	3137	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.46, 1.23]
7.1 Heparinoid versus standard UFH	4	493	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.43, 2.94]
7.2 LMWH versus standard UFH	5	2644	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.37, 1.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Symptomatic intracranial haemorrhage/haemorrhagic transformation of the infarct during treatment period	8	3102	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.35, 1.54]
8.1 Heparinoid versus standard UFH	4	493	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.19, 4.40]
8.2 LMWH versus standard UFH	4	2609	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.30, 1.60]
9 Extracranial haemorrhage during treatment period	7		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Major extracranial haemorrhage	7	3012	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.79 [1.30, 11.06]
9.2 Minor extracranial haemorrhage	7	3012	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.67, 1.24]
10 Effect of recurrent ischaemic stroke or recurrent stroke of unknown pathological type during treatment period	2	1839	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [0.61, 6.11]
10.1 LMWH versus UFH	2	1839	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [0.61, 6.11]
11 Deep venous thrombosis according to heparinoid dosage regimen	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
11.1 350 anti-Xa units 24-hourly versus 5000 IU UFH 12-hourly	1	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.11 [0.67, 6.59]
11.2 750 anti-Xa units 24-hourly versus 5000 IU UFH 12-hourly	1	72	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.54 [0.14, 2.14]
11.3 1250 anti-Xa units 24-hourly versus 5000 IU UFH 12-hourly	2	246	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.32, 1.26]
11.4 750 anti-Xa units 12-hourly versus 5000 IU UFH 12-hourly	2	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.13, 0.71]
11.5 1250 anti-Xa units 12-hourly versus 5000 IU UFH 12-hourly	1	55	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.06, 1.23]
12 Intracranial and extracranial haemorrhage during treatment according to dosage regimen	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
12.1 350 anti-Xa units 24-hourly versus 5000 IU UFH 12-hourly	1	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.29 [0.45, 3.68]
12.2 750 anti-Xa units 24-hourly versus 5000 IU UFH 12-hourly	1	72	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.33, 2.50]

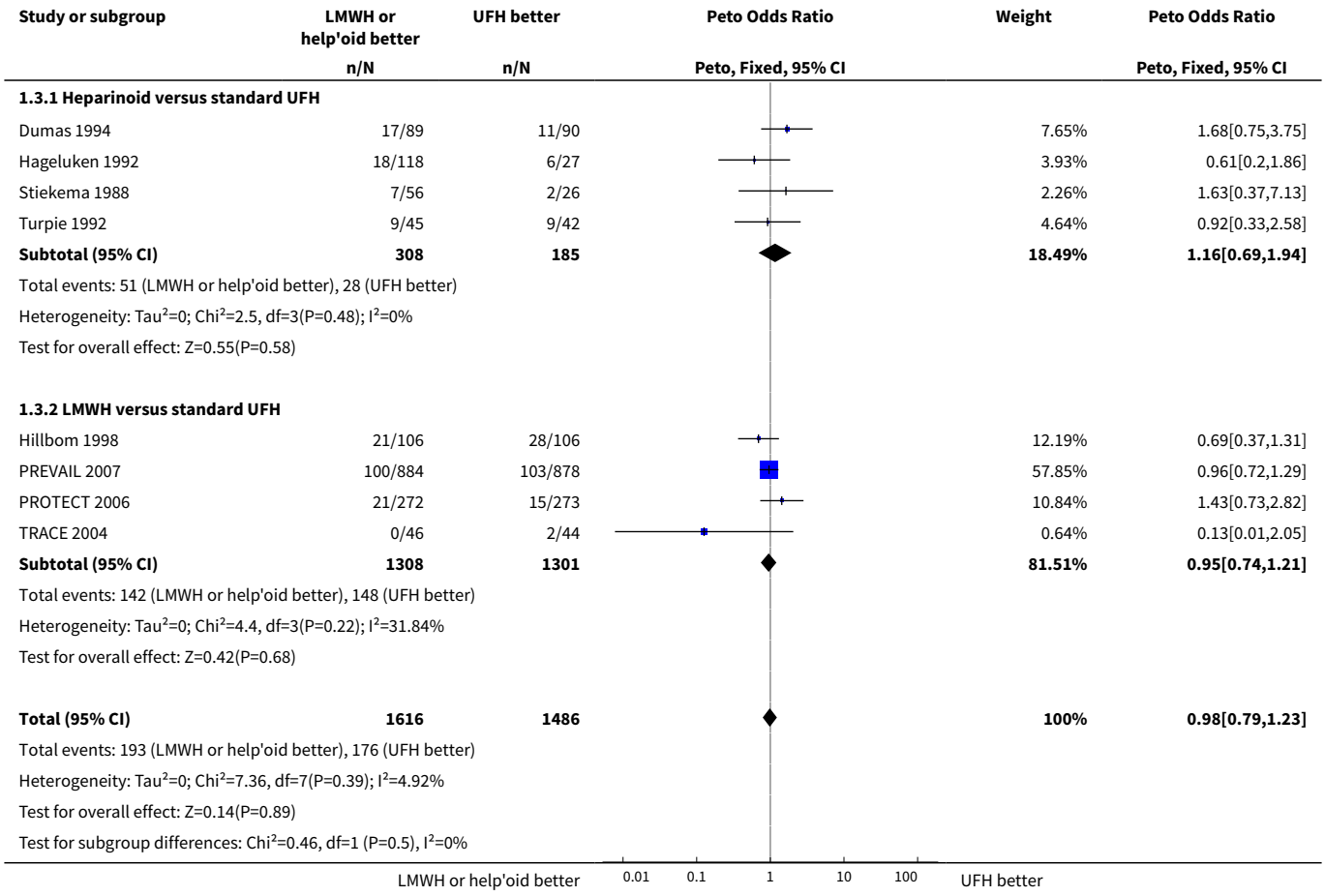
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.3 1250 anti-Xa units 24-hourly versus 5000 IU UFH 12-hourly	2	246	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.38, 1.25]
12.4 750 anti-Xa units 12-hourly versus 5000 IU UFH 12-hourly	2	138	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.73 [1.03, 7.24]
12.5 1250 anti-Xa units 12-hourly versus 5000 IU UFH 12-hourly	1	53	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.71 [0.31, 9.25]

Analysis 1.2. Comparison 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, Outcome 2 Death from all causes during treatment period.

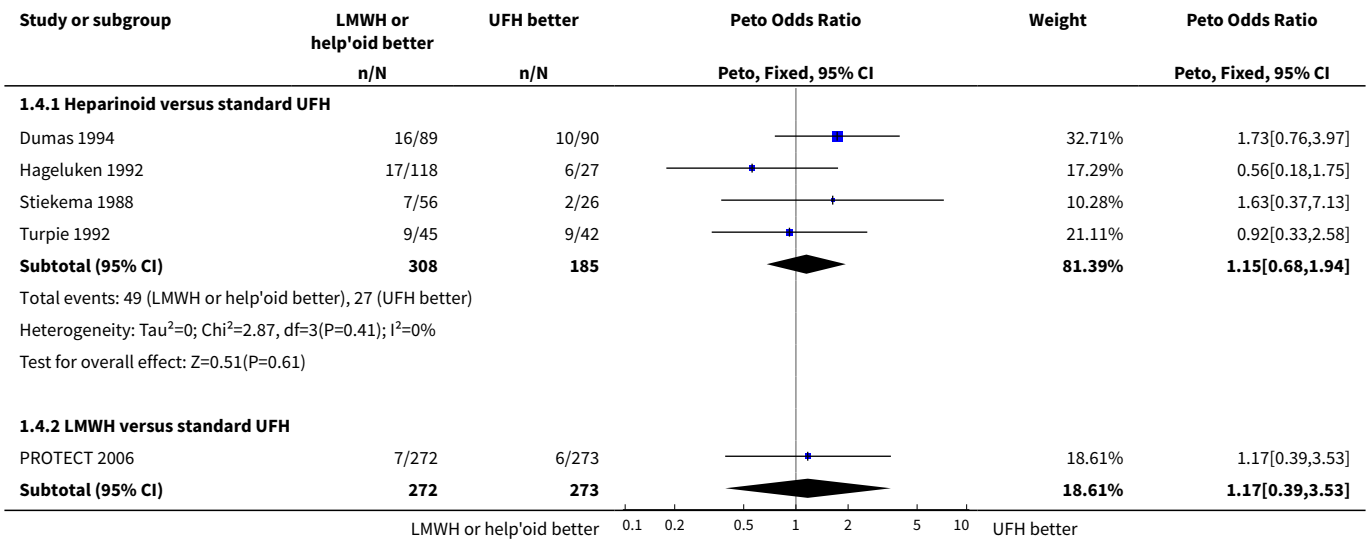
Study or subgroup	LMWH or help'oid better n/N	UFH better n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.2.1 Heparinoid versus standard UFH					
Dumas 1994	12/89	6/90		10.39%	2.12[0.8,5.59]
Hageluken 1992	11/118	4/27		5.24%	0.56[0.14,2.18]
Stiekema 1988	7/56	2/26		4.48%	1.63[0.37,7.13]
Turpie 1992	2/45	4/42		3.6%	0.46[0.09,2.38]
Subtotal (95% CI)	**308**	**185**		**23.72%**	**1.19[0.62,2.26]**
Total events: 32 (LMWH or help'oid better), 16 (UFH better)					
Heterogeneity: Tau^2=0; Chi^2=4, df=3(P=0.26); I^2=25%					
Test for overall effect: Z=0.52(P=0.6)					
1.2.2 LMWH versus standard UFH					
Hillbom 1998	9/106	8/106		10.03%	1.14[0.42,3.05]
PREVAIL 2007	48/884	45/878		56.27%	1.06[0.7,1.61]
PROTECT 2006	7/272	7/273		8.72%	1[0.35,2.9]
TRACE 2004	0/46	2/44		1.26%	0.13[0.01,2.05]
Subtotal (95% CI)	**1308**	**1301**		**76.28%**	**1.03[0.72,1.47]**
Total events: 64 (LMWH or help'oid better), 62 (UFH better)					
Heterogeneity: Tau^2=0; Chi^2=2.24, df=3(P=0.52); I^2=0%					
Test for overall effect: Z=0.15(P=0.88)					
Total (95% CI)	**1616**	**1486**		**100%**	**1.06[0.78,1.46]**
Total events: 96 (LMWH or help'oid better), 78 (UFH better)					
Heterogeneity: Tau^2=0; Chi^2=6.38, df=7(P=0.5); I^2=0%					
Test for overall effect: Z=0.39(P=0.7)					
Test for subgroup differences: Chi^2=0.15, df=1 (P=0.7), I^2=0%					

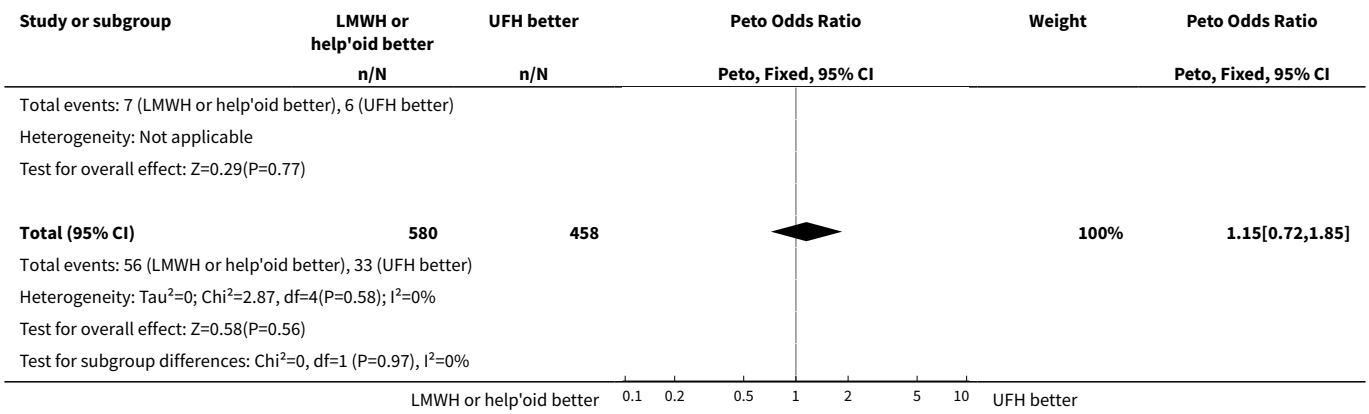


Analysis 1.3. Comparison 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, Outcome 3 Death from all causes during follow-up.

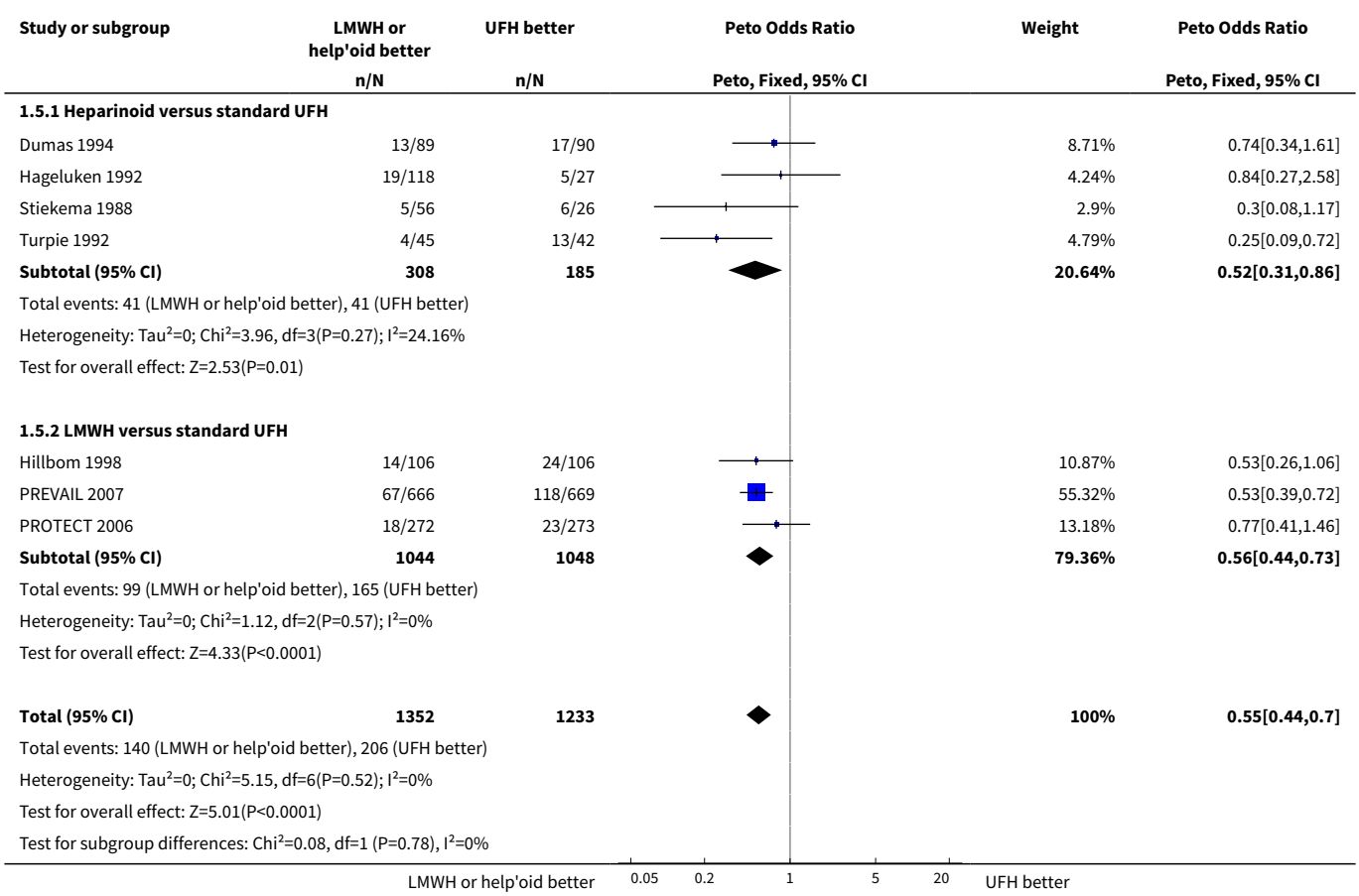


Analysis 1.4. Comparison 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, Outcome 4 Vascular death during follow-up.



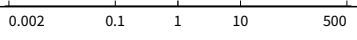


Analysis 1.5. Comparison 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, Outcome 5 Deep venous thrombosis during treatment period.



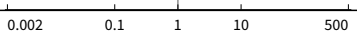
Analysis 1.6. Comparison 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, Outcome 6 Pulmonary embolism during follow-up.

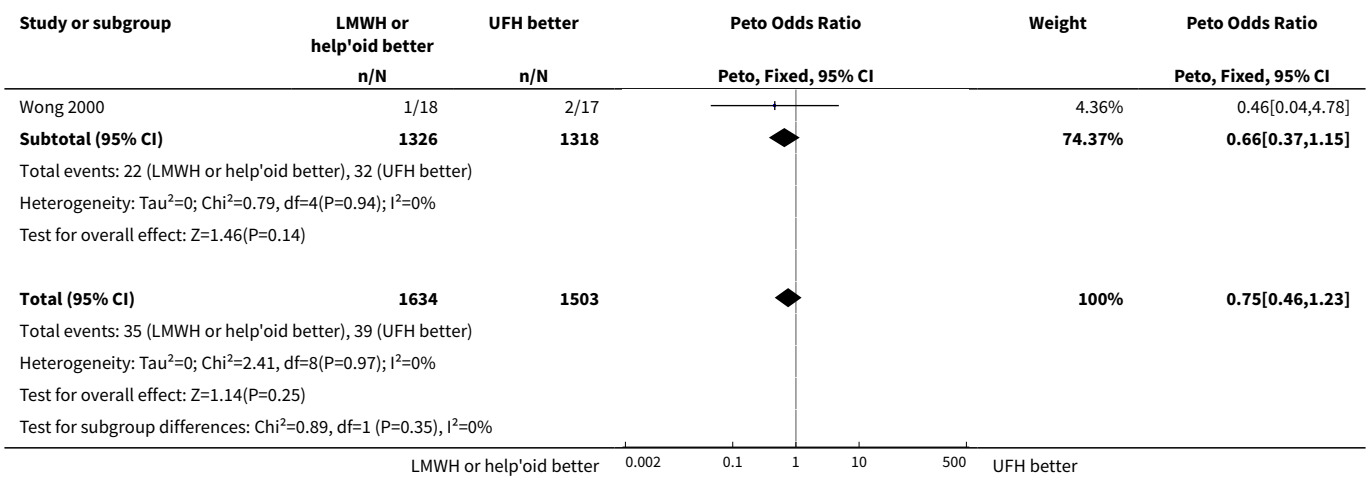
Study or subgroup	LMWH or help'oid better n/N	UFH better n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.6.1 Heparinoid versus standard UFH					
Dumas 1994	4/89	4/90		41.13%	1.01[0.25,4.16]
Hageluken 1992	1/118	1/27		6.44%	0.12[0,4.43]
Stiekema 1988	0/56	0/26			Not estimable
Turpie 1992	0/45	1/42		5.35%	0.13[0,6.37]
Subtotal (95% CI)	**308**	**185**		**52.92%**	**0.64[0.18,2.21]**
Total events: 5 (LMWH or help'oid better), 6 (UFH better)					
Heterogeneity: Tau^2=0; Chi^2=1.87, df=2(P=0.39); I^2=0%					
Test for overall effect: Z=0.71(P=0.48)					
1.6.2 LMWH versus standard UFH					
Hillbom 1998	2/106	5/106		36.4%	0.41[0.09,1.86]
PROTECT 2006	1/272	1/273		10.68%	1[0.06,16.09]
Subtotal (95% CI)	**378**	**379**		**47.08%**	**0.51[0.13,1.9]**
Total events: 3 (LMWH or help'oid better), 6 (UFH better)					
Heterogeneity: Tau^2=0; Chi^2=0.3, df=1(P=0.58); I^2=0%					
Test for overall effect: Z=1.01(P=0.31)					
Total (95% CI)	**686**	**564**		**100%**	**0.57[0.23,1.41]**
Total events: 8 (LMWH or help'oid better), 12 (UFH better)					
Heterogeneity: Tau^2=0; Chi^2=2.23, df=4(P=0.69); I^2=0%					
Test for overall effect: Z=1.21(P=0.23)					
Test for subgroup differences: Chi^2=0.06, df=1 (P=0.81), I^2=0%					



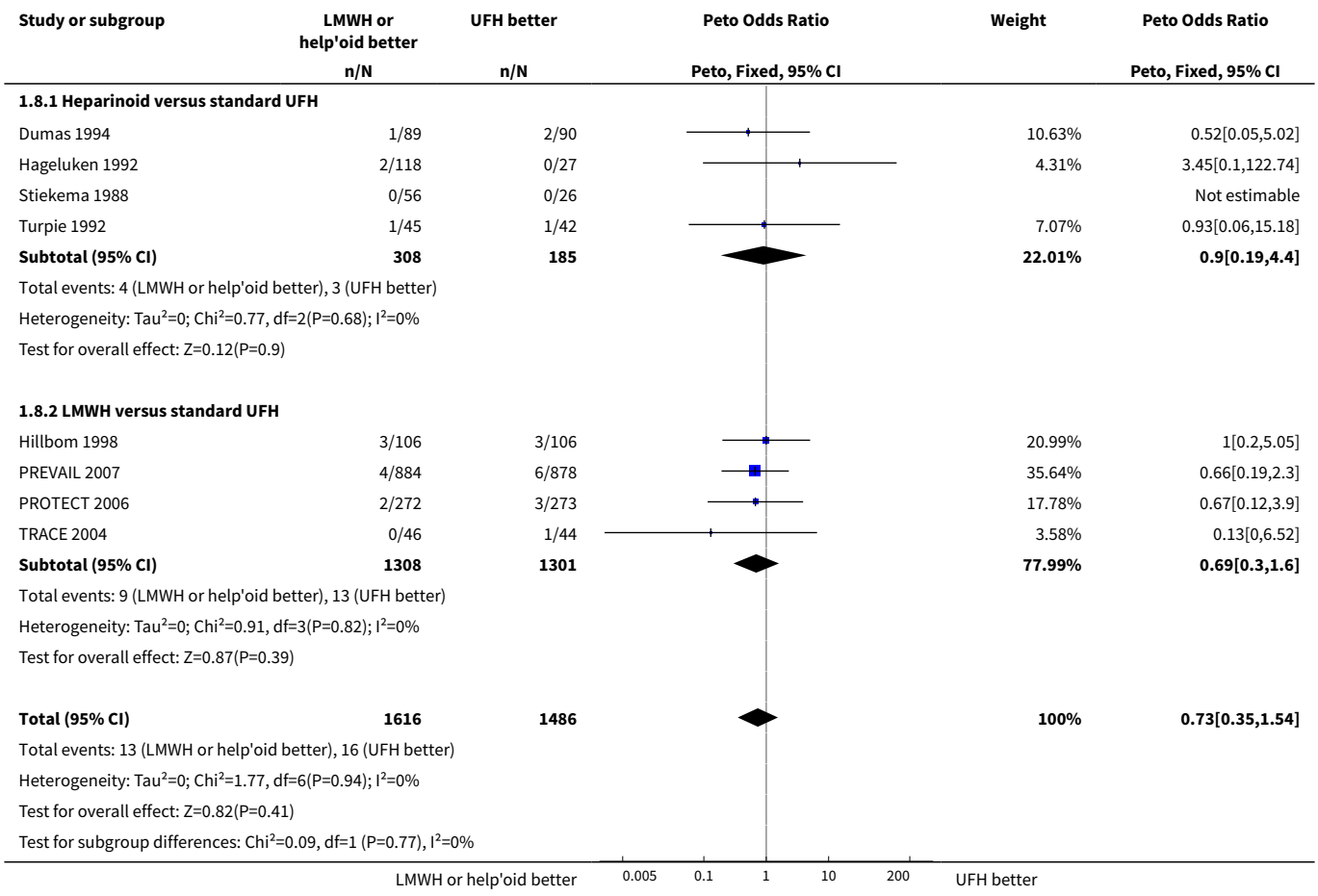
Analysis 1.7. Comparison 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, Outcome 7 Any intracranial haemorrhage/haemorrhagic transformation of the cerebral infarct during treatment period.

Study or subgroup	LMWH or help'oid better n/N	UFH better n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.7.1 Heparinoid versus standard UFH					
Dumas 1994	2/89	3/90		7.56%	0.67[0.11,3.96]
Hageluken 1992	5/118	1/27		5.43%	1.14[0.14,9.26]
Stiekema 1988	2/56	1/26		3.92%	0.93[0.08,10.86]
Turpie 1992	4/45	2/42		8.73%	1.89[0.36,9.83]
Subtotal (95% CI)	**308**	**185**		**25.63%**	**1.12[0.43,2.94]**
Total events: 13 (LMWH or help'oid better), 7 (UFH better)					
Heterogeneity: Tau^2=0; Chi^2=0.73, df=3(P=0.87); I^2=0%					
Test for overall effect: Z=0.24(P=0.81)					
1.7.2 LMWH versus standard UFH					
Hillbom 1998	15/106	20/106		45.4%	0.71[0.35,1.47]
PREVAIL 2007	4/884	6/878		15.38%	0.66[0.19,2.3]
PROTECT 2006	2/272	3/273		7.67%	0.67[0.12,3.9]
TRACE 2004	0/46	1/44		1.55%	0.13[0,6.52]





Analysis 1.8. Comparison 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, Outcome 8 Symptomatic intracranial haemorrhage/haemorrhagic transformation of the infarct during treatment period.

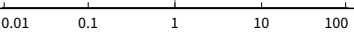


Analysis 1.9. Comparison 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, Outcome 9 Extracranial haemorrhage during treatment period.

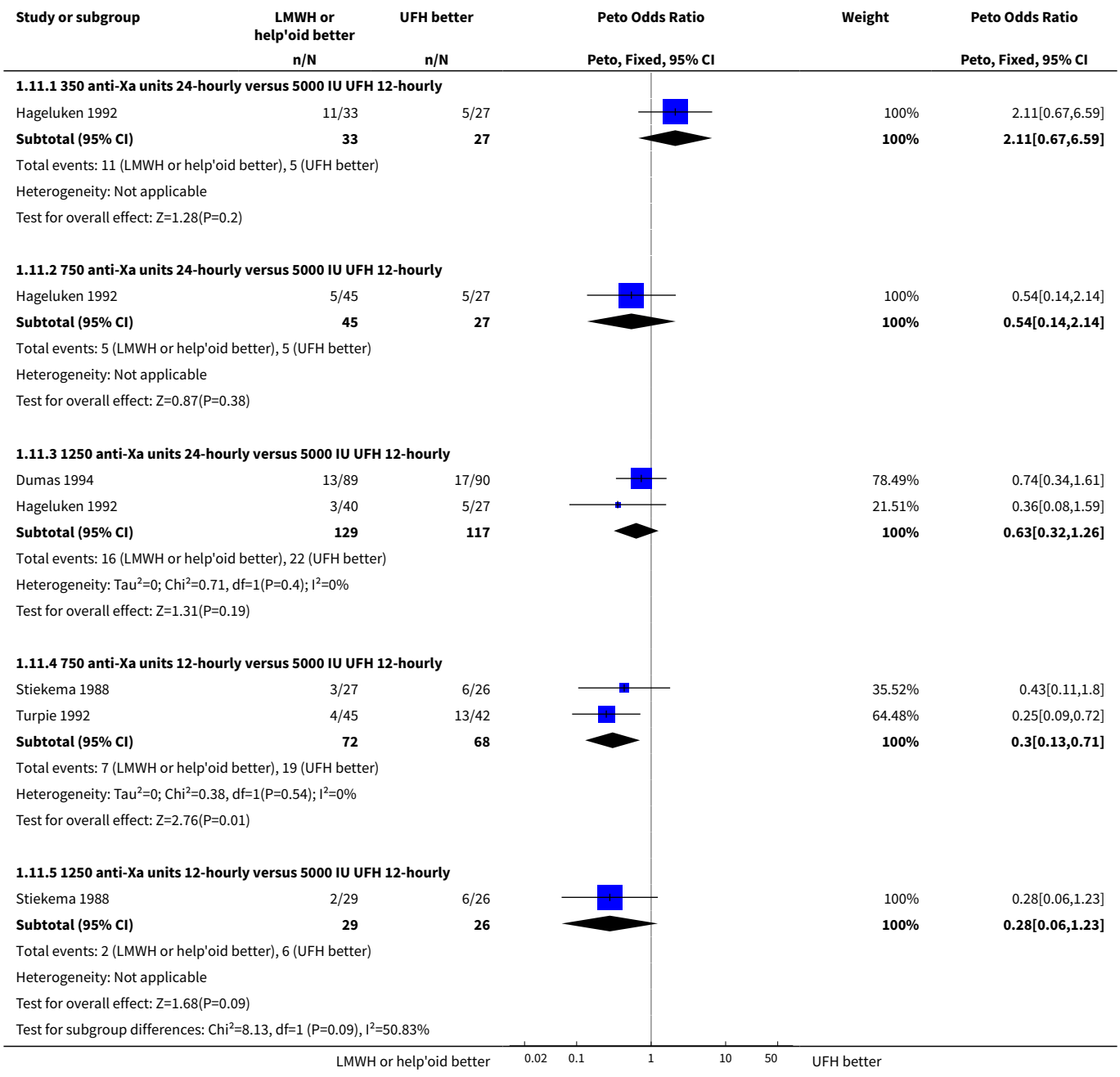
Study or subgroup	LMWH or help'oid better n/N	UFH better n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.9.1 Major extracranial haemorrhage					
Dumas 1994	1/89	0/90		7.44%	7.47[0.15,376.62]
Hageluken 1992	1/118	0/27		4.51%	3.42[0.02,525.18]
Hillbom 1998	0/106	0/106			Not estimable
PREVAIL 2007	7/884	0/878		51.92%	7.39[1.68,32.6]
PROTECT 2006	1/272	2/273		22.25%	0.51[0.05,4.96]
Stiekema 1988	1/56	0/26		6.45%	4.32[0.06,291.84]
Turpie 1992	1/45	0/42		7.43%	6.91[0.14,349.18]
Subtotal (95% CI)	**1570**	**1442**		**100%**	**3.79[1.3,11.06]**
Total events: 12 (LMWH or help'oid better), 2 (UFH better)					
Heterogeneity: Tau²=0; Chi²=3.97, df=5(P=0.55); I²=0%					
Test for overall effect: Z=2.44(P=0.01)					
1.9.2 Minor extracranial haemorrhage					
Dumas 1994	15/89	19/90		17.14%	0.76[0.36,1.6]
Hageluken 1992	29/118	8/27		10.41%	0.77[0.3,2]
Hillbom 1998	5/106	6/106		6.49%	0.83[0.25,2.77]
PREVAIL 2007	42/884	48/878		52.89%	0.86[0.56,1.32]
PROTECT 2006	7/272	5/273		7.28%	1.41[0.45,4.42]
Stiekema 1988	10/56	1/26		5.17%	3.29[0.85,12.78]
Turpie 1992	0/45	1/42		0.62%	0.13[0,6.37]
Subtotal (95% CI)	**1570**	**1442**		**100%**	**0.91[0.67,1.24]**
Total events: 108 (LMWH or help'oid better), 88 (UFH better)					
Heterogeneity: Tau²=0; Chi²=5.43, df=6(P=0.49); I²=0%					
Test for overall effect: Z=0.58(P=0.56)					
Test for subgroup differences: Chi²=6.3, df=1 (P=0.01), I²=84.12%					

Analysis 1.10. Comparison 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, Outcome 10 Effect of recurrent ischaemic stroke or recurrent stroke of unknown pathological type during treatment period.

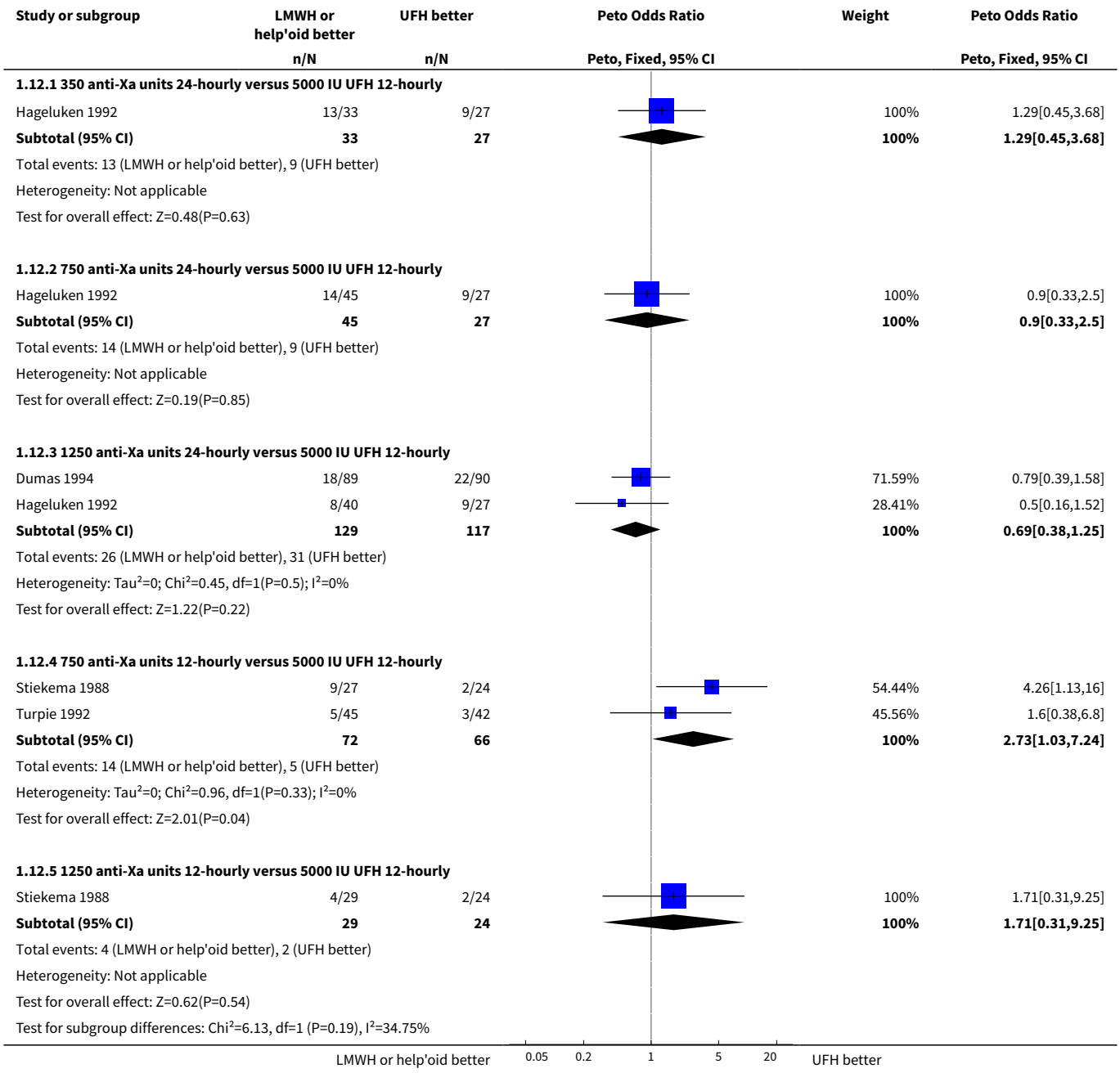
Study or subgroup	LMWH or help'oid better n/N	UFH better n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.10.1 LMWH versus UFH					
PREVAIL 2007	3/877	3/872		51.39%	0.99[0.2,4.94]
TRACE 2004	5/46	1/44		48.61%	3.92[0.75,20.37]
Subtotal (95% CI)	**923**	**916**		**100%**	**1.94[0.61,6.11]**
Total events: 8 (LMWH or help'oid better), 4 (UFH better)					
Heterogeneity: Tau²=0; Chi²=1.37, df=1(P=0.24); I²=26.94%					
Test for overall effect: Z=1.13(P=0.26)					
Total (95% CI)	**923**	**916**		**100%**	**1.94[0.61,6.11]**
Total events: 8 (LMWH or help'oid better), 4 (UFH better)					
Heterogeneity: Tau²=0; Chi²=1.37, df=1(P=0.24); I²=26.94%					
Test for overall effect: Z=1.13(P=0.26)					



Analysis 1.11. Comparison 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, Outcome 11 Deep venous thrombosis according to heparinoid dosage regimen.



Analysis 1.12. Comparison 1 LMWH/heparinoid versus standard UFH in acute ischaemic stroke, Outcome 12 Intracranial and extracranial haemorrhage during treatment according to dosage regimen.



APPENDICES

Appendix 1. CENTRAL

Heparin AND Stroke

Appendix 2. MEDLINE search strategy

The following search strategy, using a combination of controlled vocabulary and text words, was used for MEDLINE and the Cochrane Central Register of Controlled Trials.

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or cerebrovascular accident/ or exp brain infarction/ or exp hypoxia-ischemia, brain/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/
2. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
3. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
4. 1 or 2 or 3
5. exp Heparin, Low-Molecular-Weight/
6. (low molecular weight heparin$ or low-molecular-weight heparin$ or lmwh$).tw.
7. (antixarin or ardeparin or bemiparin or certoparin or cy 222 or dalteparin or embolex or enoxaparin or fondaparin$ or idraparinux or monoembolex or nadroparin or parnaparin or rd 11885 or reviparin or tedelparin or tinzaparin).tw.
8. Heparinoids/
9. (heparinoid$ or atheroid or danaparoid or org 10172 or mesoglycan or dermatan sul$ or heparan sul$ or pentosan polysul$).tw.
10. or/5-9
11. 4 and 10

Appendix 3. Embase search strategy

The following search strategy, using a combination of controlled vocabulary and text words, was used for EMBASE.

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or carotid artery disease/ or carotid artery obstruction/ or carotid artery thrombosis/ or internal carotid artery occlusion/ or brain infarction/ or brain infarction size/ or brain stem infarction/ or cerebellum infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/ or stroke patient/
2. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
3. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
4. 1 or 2 or 3
5. exp Low Molecular Weight Heparin/
6. (low molecular weight heparin$ or low-molecular-weight heparin$ or lmwh$).tw.
7. (antixarin or ardeparin or bemiparin or certoparin or cy 222 or dalteparin or embolex or enoxaparin or fondaparin$ or idraparinux or monoembolex or nadroparin or parnaparin or rd 11885 or reviparin or tedelparin or tinzaparin).tw.
8. heparinoid/
9. (heparinoid$ or atheroid or danaparoid or org 10172 or mesoglycan or dermatan sul$ or heparan sul$ or pentosan polysul$).tw.
10. or/5-9
11. 4 and 10

Appendix 4. Trials registers

The following registers were searched with the terms heparin AND stroke

- ClinicalTrials.gov (clinicaltrials.gov/)
- EU Clinical Trials Register (clinicaltrialsregister.eu/ctr-search/search)
- Stroke Trials Registry (strokecenter.org/trials/).
- ISRCTN Registry (isrctn.com/)
- WHO International Clinical Trials Registry Platform (who.int/ictrp/en/)

F E E D B A C K

Feedback on the 2004 version of this review

Summary

If unfractionated heparin (UFH) does not benefit patients with acute ischaemic stroke, why do a review where UFH is the control intervention? Although low-molecular-weight heparins/heparinoids (LMWH) do not reduce death or disability (but do increase intracranial bleeding), should the 'Implications for practice' justify LMWH in some case of acute ischaemic stroke in view of their reduction of deep vein thrombosis (and probably pulmonary embolism) in comparison with UFH? Similarly, are further trials of anticoagulant ethical?

Reply

The first version of the review was prepared at a time when there was uncertainty about the overall effects of heparins in acute ischaemic stroke. Since then, as the commenter states, evidence has emerged which shows that there is no net benefit from the immediate anticoagulation in this setting. However, as is often the case, this evidence did not alter the beliefs of some clinicians, and hence, heparin is still used in some countries, in certain types of patient with acute ischaemic stroke, for specific reasons and especially for prevention of venous thrombo-embolism.

This review is now based on the premise that if a clinician plans to treat a patient for some special reason with some form of heparin then the choice of agent should be evidence based. The wording of the 'Implications for practice' and 'Implications for research' sections reflect this.

I should point out that this review is currently being updated, and we have identified three further trials comparing LMWH with UFH in acute stroke, which testifies to the belief among some clinicians in the value of this form of treatment. The emergence of new evidence is a good reason to keep the review up to date.

Contributors

Commenter: David K Cundiff, MD (22 June 2007)
Reply: Professor Peter Sandercock (9 July 2007)

WHAT'S NEW

Date	Event	Description
8 February 2017	New citation required but conclusions have not changed	Conclusions not changed.
8 February 2017	New search has been performed	New author added. Searches updated. Background section revised, updated and new references added. Primary objective for review and primary outcome defined. Searches updated, PRISMA diagram added. We identified no new studies: the review has nine included studies involving 3137 participants. We have edited and updated the text and added 'Risk of bias' tables and a 'Summary of findings' table.

HISTORY

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

Date	Event	Description
7 March 2011	Feedback has been incorporated	Link to feedback added.
28 July 2008	Amended	Previous feedback on the 2004 version of this review (published in Issue 2, 2005) has been re-incorporated. See Feedback section.
14 March 2008	Amended	Converted to new review format.
3 March 2008	New citation required but conclusions have not changed	There has been a change in authorship.
15 September 2007	New search has been performed	We updated the searches to June 2007 and included three new studies (TRACE 2004, PROTECT 2006, PREVAIL 2007) with 2397 patients. The total number of included trials is now nine with 3137 participants. The review has been edited extensively.

CONTRIBUTIONS OF AUTHORS

TL ran the searches, TL and PS selected studies, extracted data and wrote the revised text for this update

DECLARATIONS OF INTEREST

Peter Sandercock: principal investigator of the International Stroke Trial. In the distant past, he received Honoraria (paid to the department) and travel expenses from a variety of pharmaceutical companies (including Organon) for giving lectures at medical conferences. He is not involved in any contractual consultancies with any company; he is not on the speakers panel of any company.

Tze Shin Leong: none known

SOURCES OF SUPPORT

Internal sources

- University of Edinburgh, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this update, the Background was revised, updated and new references added. For consistency with other Cochrane Stroke Group reviews, we defined a single primary objective for the review and consequently selected a single primary outcome. The main search strategies were reviewed and search terms updated (Appendix 1; Appendix 2; Appendix 3; Appendix 4). No changes to the methods of analysis were required. A PRISMA diagram was added (Figure 1). We added funnel plots (Figure 4; Figure 5). We rechecked all included studies and evaluated the risk of bias for each study in greater detail. We added 'Risk of bias' tables. We also conducted GRADE assessment and included Summary of findings for the main comparison. The analytic methods did not change.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anticoagulants [*therapeutic use]; Brain Ischemia [drug therapy]; Cause of Death; Fibrinolytic Agents [*therapeutic use]; Hemorrhage [chemically induced] [epidemiology]; Heparin [therapeutic use]; Heparin, Low-Molecular-Weight [*therapeutic use]; Heparinoids [*therapeutic use]; Pulmonary Embolism [epidemiology]; Randomized Controlled Trials as Topic; Stroke [*drug therapy] [mortality]; Venous Thrombosis [epidemiology]

MeSH check words

Humans