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Antithrombotic treatment after stroke due to intracerebral haemorrhage (Review)

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[Intervention Review]

Antithrombotic treatment after stroke due to intracerebral haemorrhage

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ABSTRACT

Background

Survivors of stroke due to intracerebral haemorrhage (ICH) are at risk of thromboembolism. Antithrombotic (antiplatelet or anticoagulant) treatments may lower the risk of thromboembolism after ICH, but they may increase the risks of bleeding.

Objectives

To determine the overall effectiveness and safety of antithrombotic drugs for people with ICH.

Search methods

We searched the Cochrane Stroke Group Trials Register (24 March 2017). We also searched the Cochrane Central Register of Controlled Trials (CENTRAL: the Cochrane Library 2017, Issue 3), MEDLINE Ovid (from 1948 to March 2017), Embase Ovid (from 1980 to March 2017), and online registries of clinical trials (8 March 2017). We also screened the reference lists of included trials for additional, potentially relevant studies.

Selection criteria

We selected all randomised controlled trials (RCTs) of any antithrombotic treatment after ICH.

Data collection and analysis

Three review authors independently extracted data. We converted categorical estimates of effect to the risk ratio (RR) or odds ratio (OR), as appropriate. We divided our analyses into short- and long-term treatment, and used fixed-effect modelling for meta-analyses. Three review authors independently assessed the included RCTs for risks of bias and we created a 'Summary of findings' table using GRADE.

Main results

We included two RCTs with a total of 121 participants. Both RCTs were of short-term parenteral anticoagulation early after ICH: one tested heparin and the other enoxaparin. The risk of bias in the included RCTs was generally unclear or low, with the exception of blinding of participants and personnel, which was not done. The included RCTs did not report our chosen primary outcome (a composite outcome of all serious vascular events including ischaemic stroke, myocardial infarction, other major ischaemic event, ICH, major extracerebral haemorrhage, and vascular death). Parenteral anticoagulation did not cause a statistically significant difference in case fatality (RR

1.25, 95% confidence interval (CI) 0.38 to 4.07 in one RCT involving 46 participants, low-quality evidence), ICH, or major extracerebral haemorrhage (no detected events in one RCT involving 75 participants, low-quality evidence), growth of ICH (RR 1.64, 95% CI 0.51 to 5.29 in two RCTs involving 121 participants, low-quality evidence), deep vein thrombosis (RR 0.99, 95% CI 0.49 to 1.96 in two RCTs involving 121 participants, low quality evidence), or major ischaemic events (RR 0.54, 95% CI 0.23 to 1.28 in two RCTs involving 121 participants, low quality evidence).

Authors' conclusions

There is insufficient evidence from RCTs to support or discourage the use of antithrombotic treatment after ICH. RCTs comparing starting versus avoiding antiplatelet or anticoagulant drugs after ICH appear justified and are needed in clinical practice.

PLAIN LANGUAGE SUMMARY

Drugs to prevent clots after bleeding in the brain

Review question

What is the effectiveness and safety of medications used to prevent clots (antithrombotic treatments) both in the early stages and long-term in people who have had a bleed within their brain (intracerebral haemorrhage)?

Background

People with stroke due to bleeding in the brain (also known as intracerebral haemorrhage: ICH) are more likely to develop clots in their blood vessels due to immobility (in the early stages) and due to other medical conditions (in the long term). Blood clots in the lungs, brain, or other organs can cause serious illness or death. Drugs that prevent clots (also known as 'antithrombotic drugs') might be useful to stop clot formation in people with ICH. However, these drugs can also cause serious bleeding complications.

Study characteristics

From extensive searches conducted on 8 March 2017, we identified two relevant randomised controlled trials (RCTs), which are the fairest tests of treatment. There were 121 participants in these two trials, which compared blood-thinning 'anticoagulant' drugs (heparin in one and enoxaparin in the other) delivered by injections under the skin versus no anticoagulant drug soon after ICH.

Key results

The primary outcome of this review was the combined risk of several important clinical outcome events (such as another intracerebral haemorrhage, ischaemic stroke, or death from a cardiovascular cause). We were not able to calculate this outcome for the included studies. Neither RCT reported on recovery of independence or mental abilities. One RCT involving 46 participants reported on case fatality associated with short-term antithrombotic treatment, and did not find a statistically meaningful effect. For the consequences of treatment that could be analysed, the risk estimates were imprecise and uncertain. Therefore, the potential benefits and harms of antithrombotic drugs soon after a stroke due to bleeding in the brain remain unclear. New high-quality RCTs investigating the use of antithrombotic treatment after stroke due to ICH appear justified and are needed.

Quality of the evidence

The overall quality of the evidence was low. This is due to the way the included trials were conducted and reported, as well as the small number of participants, which may not have been high enough to detect small differences between the antithrombotic treatment and no antithrombotic treatment groups.

Summary of findings for the main comparison. Antithrombotic treatment compared to no antithrombotic treatment for intracerebral haemorrhage

Short-term antithrombotic treatment

Patient or population: people with intracerebral haemorrhage
Setting: any
Intervention: antithrombotic treatment (parenteral anticoagulation)
Comparison: no antithrombotic treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no antithrombotic treatment	Risk with Antithrombotic treatment				
Composite vascular endpoint	Study population		not estimable	(0 studies)	-	We were unable to calculate the composite endpoint because no included study reported all component endpoints.
Death	Study population		RR 1.25 (0.38 to 4.07)	46 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	-
	174 per 1,000	217 per 1,000 (66 to 708)				
Growth of ICH	Study population		RR 1.64 (0.51 to 5.29)	121 (2 RCTs)	⊕⊕⊖⊖ LOW [1,2]	-
	51 per 1,000	83 per 1,000 (26 to 269)				
ICH	Study population		not estimable	75 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	-
	0 per 1,000	0 per 1,000 (0 to 0)				
Major extracerebral haemorrhage	Study population		not estimable	75 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	-
	0 per 1,000	0 per 1,000				

		(0 to 0)				
Deep vein thrombosis	Study population		RR 0.99 (0.46 to 1.96)	121 (2 RCTs)	⊕⊕⊖⊖ LOW [1,2]	-
	186 per 1,000	185 per 1,000 (86 to 365)				
Other major ischaemic events	Study population		RR 0.54 (0.23 to 1.28)	121 (2 RCTs)	⊕⊕⊖⊖ LOW [1,2]	-
	186 per 1,000	101 per 1,000 (43 to 239)				

*__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;

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]This included RCT/s has serious risk of bias due to it not describing random sequence generation or allocation concealment, as well as lack of blinding.
[2]The optimal information size (OIS) criterion is not met. The sample size of this study is probably lower than the minimum number of participants required for a trial adequately powered to identify a statistically significant difference for this outcome.

BACKGROUND

Description of the condition

Stroke due to spontaneous (non-traumatic) intracerebral haemorrhage (ICH) is caused by the extravasation of blood into brain parenchyma following rupture of a cerebral artery or arteriole. The Global Burden of Disease (GBD) Study estimated that in the world in 2010 there were 5.32 million incident (first ever) haemorrhagic strokes (i.e. ICH and subarachnoid haemorrhage), resulting in an incidence of 82 (95% confidence interval (CI) 72 to 93) per 100,000 person-years (Krishnamurthi 2010). Hypertension is the strongest risk factor for ICH, with a population attributable risk of approximately 50% (O'Donnell 2016). Over recent decades, the prevalence of the use of antithrombotic (antiplatelet or anticoagulant) drug use at the time of ICH has increased to approximately 50% (Béjot 2013; Lovelock 2007). Population-based case-control studies report that, among people with ICH, about 20% were taking anticoagulants and 30% were taking antiplatelet agents at the onset of symptoms, whereas among populations free of ICH, about 6% were taking anticoagulants and about 23% were taking antiplatelet agents (Lauer 2013).

Survivors of ICH are at risk of recurrent ICH, particularly if the underlying cause of the incident ICH is not treated (e.g. hypertension, arteriovenous malformation). They are also at risk of ischaemic stroke, ischaemic heart disease, atrial fibrillation, and systemic embolism.

A review of observational studies found that the annual risk of recurrent ICH was between 1.8% and 7.4% (Poon 2014). Three studies compared outcomes after ICH in different locations within the brain, two of which found that the risk of recurrence after lobar ICH appeared higher than after deep ICH (Poon 2014). Most patients in the world have ICH diagnosis and location confirmed by computed tomography (CT). However, some patients have magnetic resonance imaging (MRI), on which brain microbleeds are biomarkers of a higher risk of both recurrent ischaemic stroke and ICH (Cordonnier 2007; Wilson 2016). In studies that quantified the risks of both recurrent ICH and ischaemic stroke after ICH, these risks appeared similar (Poon 2014).

Description of the intervention

Antithrombotic (anticoagulant and antiplatelet) drugs are effective for preventing thrombosis and embolism of clots in the brain, heart, limbs, and lungs. However, their effects are unknown in people who also have a past history of ICH, because they were excluded from the RCTs that demonstrated the benefits of antithrombotic drugs. There is uncertainty about whether to start these drugs after ICH (Al-Shahi Salman 2014; Falcone 2014; Molina 2011; Steiner 2011).

Consequently, there is variation in clinical practice: the proportion of patients starting antithrombotic drugs after ICH varies from 11% to 45% in different countries (Pasquini 2014).

The indications for restarting antithrombotic drugs after ICH may include the presence of prevalent risk factors for thromboembolism (e.g. atrial fibrillation, valvular heart disease, and atherosclerosis). The indications for starting antithrombotic drugs for the first time after ICH may include new risk factors for thromboembolism (e.g. immobility, or new atrial fibrillation) or vaso-occlusive events (e.g. deep vein thrombosis and pulmonary embolism). Antithrombotic drugs after ICH can be given for prophylaxis over the short term (e.g. immobility during the period of hospitalisation following ICH) with low doses of low-molecular-weight heparin or unfractionated heparin, or over the long term (e.g. atrial fibrillation, previous vaso-occlusive disease) with oral antiplatelet or full-dose oral anticoagulant drugs.

Why it is important to do this review

A previous systematic review identified three RCTs that included a subset of people who received antithrombotic treatment after ICH, but it did not identify any clear benefits or harms of doing so (Keir 2002).

Some observational studies have addressed the use of antithrombotic drugs after ICH, but did not identify associations with beneficial or adverse outcomes that were large enough to preclude the need for RCTs (Chao 2016; Chong 2012; Claassen 2008; De Vleeschouwer 2005; Flynn 2010a; Hawryluk 2010; Kuramatsu 2015; Nielsen 2015; Pennlert 2016; Poli 2014; Viswanathan 2006).

Whether and when to use antithrombotic drugs after ICH was identified as a dilemma in the European Stroke Organisation's recent ICH guideline (Steiner 2014), which was unable to make any strong recommendations about the use of these drugs.

OBJECTIVES

Primary objective

To determine the overall effectiveness and safety of antithrombotic drugs for people with ICH.

Secondary objective

To determine whether the effectiveness and safety of antithrombotic treatment differs in prespecified subgroups (see Subgroup analysis and investigation of heterogeneity).

METHODS

Criteria for considering studies for this review

Types of studies

We sought all RCTs that made comparisons of starting versus avoiding antithrombotic drugs, or direct comparisons of different classes of antithrombotic drugs, for preventing thromboembolism after ICH. We included RCTs published in any language and planned to arrange translation where the language of publication was not English.

Types of participants

We sought RCTs whose participants survived a spontaneous ICH that had been diagnosed by CT or MRI. We included RCTs whether or not they had taken antithrombotic drugs at the time of ICH.

Types of interventions

We sought RCTs that compared the use of any antithrombotic drug against no antithrombotic treatment, as well as RCTs that compared different antithrombotic drugs. We placed no constraints on dosage, route of administration, or duration of administration. We separated RCTs investigating short-term treatment (for example, with low-molecular-weight heparin or unfractionated heparin in the acute post-stroke phase) and

those investigating long-term treatment (for example, with oral anticoagulants or antiplatelets).

We excluded RCTs in which the effects of antithrombotic drugs might have been confounded by the administration of another active drug to participants (e.g. if allocation to this additional treatment was not evenly distributed between groups in an RCT, or was not randomly allocated).

Types of outcome measures

Primary outcomes

- Composite outcome of 'all serious vascular events' (ischaemic stroke, myocardial infarction, other major ischaemic event, ICH, major extracerebral haemorrhage, and vascular death) during the scheduled follow-up period.

Secondary outcomes

- Death during the scheduled follow-up period.
- The individual components of the composite vascular outcome: ischaemic stroke, myocardial infarction, other major ischaemic event, ICH, major extracerebral haemorrhage, and vascular death.
- Growth of ICH.
- Deep vein thrombosis.
- Functional status (where measured using validated scales) at the end of the scheduled follow-up period.
- Cognitive status (where measured using validated scales) at the end of the scheduled follow-up period.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We searched for RCTs in any language and planned to arrange for the translation of relevant articles where necessary.

Electronic searches

We searched the Cochrane Stroke Group trials register in March 2017 and the following electronic databases, using search strategies that the Cochrane Stroke Group's Information Specialist helped us design:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 3) in the Cochrane Library (searched 8 March 2017) (Appendix 1);
- MEDLINE Ovid (1946 to 8 March 2017) (Appendix 2);
- Embase Ovid (1974 to 8 March 2017) (Appendix 3).

We also searched the following trials registers:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 2 March 2017) (Appendix 4);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch; searched 2 March 2017) (Appendix 4);
- ISRCTN Registry (www.isrctn.com; searched 2 March 2017) (Appendix 4);
- Stroke Trials Registry – the Internet Stroke Center (www.strokecenter.org/trials/; searched 2 March 2017) (Appendix 4).

Searching other resources

We screened the reference lists of relevant studies to identify further studies for potential inclusion in the review. We also used the Science Citation Index Cited Reference Search for forward tracking of relevant articles.

Data collection and analysis

Selection of studies

Three review authors (LAP, JB, EF) independently screened the titles and abstracts of the references obtained as a result of our searching activities, and excluded reports that were obviously irrelevant. We retrieved full-text articles for the remaining references, and the same three review authors independently screened these full-text articles to identify studies for inclusion, and identified and recorded reasons for the exclusion of ineligible studies. We resolved any disagreements through discussion or, if required, we planned on consulting a fourth review author (EB). We collated multiple reports of the same study so that each study, not each reference, is the unit of interest in the review. We recorded the selection process and completed a PRISMA flow diagram (See Figure 1 in the Results of the search section).

Data extraction and management

Three review authors (LAP, JB, EF) independently extracted data from included studies using a preformulated data collection form.

Assessment of risk of bias in included studies

Three review authors (LAP, JB, EF) independently assessed risks of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another review author (EB). We assessed the risks of bias according to the following domains.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other potential bias

We graded the risk of bias for each domain as high, low or unclear and provide information from the study report, together with a justification for our judgement, in the 'Risk of bias' tables.

Measures of treatment effect

We intended to:

- convert categorical estimates of effect to the risk ratio (RR) or odds ratio (OR), if required;
- express measures of survival as a hazard ratio (HR); and
- use summary measures obtained from univariate or, where RCTs used the same covariates for adjustment, multivariable analyses.

Unit of analysis issues

Repeated observations on participants

We planned to analyse functional and cognitive status at end of follow-up, and not to use repeat observations during follow-up. If one RCT (or only a few RCTs) had a much longer period of follow-up than the majority of RCTs (for example, two years compared with six months in the majority of trials) we intended to perform a sensitivity analysis using the six-month observations from all RCTs.

Events that may recur

We analysed the first event in all participants, and not later events.

Multiple intervention groups

Where a RCT contained multiple treatment groups that were all compared with just one control group, we intended to ensure that the placebo group was shared between the multiple treatment groups by dividing it into the appropriate number of subgroups and conducting separate, independent comparisons.

Dealing with missing data

We contacted RCT authors for unpublished data if relevant data were missing. If only a minority (less than half) of data were missing, we planned to ignore the missing data and perform a 'complete set analysis'. If more substantial amounts of data were missing, and there was a chance that data were not missing at random, we planned to perform sensitivity analyses assuming both a best-case and a worst-case scenario, or apply statistical imputation or models, or both, to account for the missing data. A best-case scenario meant that we assumed that all missing data in the intervention group represent good outcomes and all missing data in the control group represent poor outcomes. A worst-case scenario meant that we assumed that all missing data in the intervention group represent poor outcomes and all missing data in the control group represent good outcomes.

Assessment of heterogeneity

We investigated inconsistency between included RCTs using the I^2 statistic. We interpreted this value using the guide provided in Chapter 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: represents considerable heterogeneity

If we observed substantial inconsistency in our data, we intended to use sensitivity analysis to elucidate which factors might explain the inconsistency.

Assessment of reporting biases

We included all published and unpublished data and secondary publications from RCTs. If we included a sufficient number of RCTs (more than 10), we planned to assess the likelihood of reporting biases through the use of a funnel plot.

Data synthesis

If RCTs were sufficiently similar, we planned to conduct a meta-analysis by pooling the appropriate data using Review Manager 5 (RevMan 2014). We planned to calculate the risk ratio (RR), odds ratio (OR), or hazard ratio (HR) for each outcome from data extracted from included RCTs using the Peto fixed-effect method, or a random-effects model if there was significant heterogeneity between RCTs. We defined significant heterogeneity as substantial clinical or methodological diversity between RCTs such that the true effect measure is no longer uniform.

'Summary of findings' table

We created a 'Summary of findings' table using the GRADEpro Guideline Development Tool (GRADEpro GDT), and included the following outcomes for short-term antithrombotic treatment: the composite outcome of all serious vascular events, death, growth of ICH, ICH, major extracerebral haemorrhage, deep vein thrombosis, other major ischaemic events, functional status, and cognitive status. We planned a 'Summary of findings' table for long-term antithrombotic treatment which included the following outcomes: the composite outcome of all serious vascular events, death, functional status, and cognitive status. Two review authors (LAP, JB) independently classified the quality of the evidence as being 'high', 'moderate', 'low', or 'very low', based on the presence and extent of the following five criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- Limitations in the design and implementation of the contributing trials
- Indirectness of evidence
- Unexplained heterogeneity or inconsistency of results
- Imprecision of results
- High probability of publication bias

We provided justification in the footnotes when we downgraded the quality from 'high'.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analyses, if possible.

- Participants with different age, sex, and stroke severity
- Different classes of antithrombotic drugs
- Different intensities of antithrombotic treatment
- Different times of starting treatment (e.g. within one month of ICH versus later, or within 10 to 30 weeks or later)
- Participants who were on antithrombotic treatment before ICH (re-starters) versus participants who were not receiving these treatments (starters)
- Different levels of risk for future ischaemic events (for example, because of differences in age, sex, history of hypertension, history of atrial fibrillation (with further stratification by the CHA_2DS_2-Vasc score))
- Different levels of risk for future ICH
- Biomarkers of bleeding or clotting risk on brain CT or MRI (e.g. brain microbleeds on MRI)

Sensitivity analysis

If the results were heterogeneous, we planned to use sensitivity analysis to investigate how the results differed when we excluded RCTs that were found to have a high risk of bias. We planned to perform other sensitivity analyses to explore reasons for

heterogeneity, for example, where there is an active therapy other than an antithrombotic drug that is not balanced by the randomisation process.

RESULTS

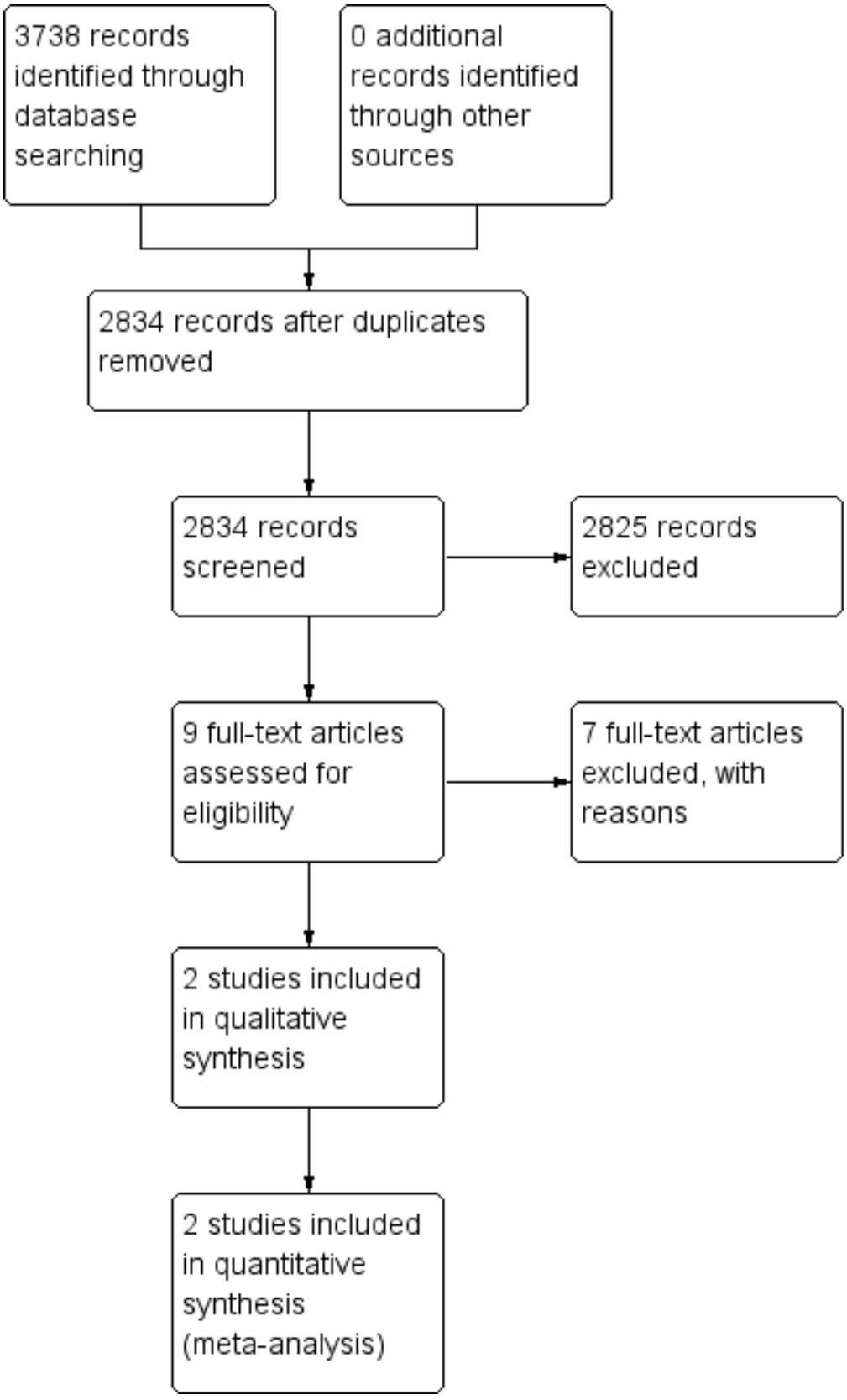
Description of studies

We included two RCTs (see Included studies), excluded seven RCTs (see Excluded studies), and identified seven ongoing RCTs (see Ongoing studies). For comprehensive tabulated descriptions of included, excluded, and ongoing studies please refer to Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies.

Results of the search

Our searches of CENTRAL, Embase, and OVID MEDLINE identified 331, 2557, and 850 potentially relevant records, respectively. Automated de-duplication identified 904 redundant records, leaving 2834 unique and potentially relevant records. We screened the titles and abstracts of these 2834 records and assessed the full texts of nine relevant records for inclusion (Boeer 1991; CAST 1997; Dickmann 1988; Frontera 2014; IST 1997; Li 2013; Orken 2009; Venturelli 2014; Yan 2014). We included two RCTs in our review (Dickmann 1988; Orken 2009). A reference search of included RCTs yielded no further relevant records. See Figure 1 for a graphical representation of our search.

Figure 1. Study flow diagram.



The search of trials registries for ongoing RCTs identified three relevant RCTs: APACHE-AF; PICASSO; RESTART, and we were aware of four additional RCTs from personal communication with investigators (NASPAF-ICH; RESTART Nord de France; SoSTART; STATICH).

Included studies

Dickmann 1988 was a German single-centre study that excluded patients if they had a bleeding diathesis, a sustained diastolic blood pressure higher than 120 mmHg or were in deep coma with signs of brain herniation, and retained 46 participants for inclusion.

Orken 2009 was a Turkish single-centre study that started with 110 ICH patients and applied the following exclusion criteria: early death before heparin treatment (n = 13), death before day 7 investigations (n = 4), secondary ICH due to aneurysm, arteriovenous malformations, trauma, or tumour (n = 11), excessive anticoagulation (International normalised ratio (INR) > 2.0) (n = 5), and contraindication to contrast media (n = 2). This left 75 participants for inclusion.

Both of the included RCTs included participants with ICH diagnosed by CT. Orken 2009 specified that these were primary ICH, whereas Dickmann 1988 did not specify the type of ICH included. Dickmann 1988 used 5000 units of heparin (Liquemin-Roche) delivered subcutaneously every eight hours starting at day four after ICH. Orken 2009 used 40 mg/day of enoxaparin sodium delivered subcutaneously after the first 48 hours from ICH onset. The intervention and comparator groups of both RCTs received graduated compression stockings. Dickmann 1988 reported on other major ischaemic events, and vascular death from other causes, although did not specifically define these outcomes. Orken 2009 reported on other major ischaemic events, ICH, and major extracerebral haemorrhage. Both of the included RCTs provided short-term outcome data only. Dickmann 1988 had a follow-up period of 10 days and Orken 2009 had a follow-up period of 21 days.

Excluded studies

We excluded seven studies for not meeting the inclusion criteria of this review after having screened their full texts.

Boeer 1991 was an extension phase of Dickmann 1988 and randomisation was not described, leading to its exclusion from this review. CAST 1997 and IST 1997 were two RCTs investigating the use of antiplatelet treatment after acute ischaemic stroke, and included several hundred participants with ICH who were randomised before CT had been performed to establish the pathological sub-type of stroke. Data on the ICH sub-population of these studies were reported in a systematic review (Keir 2002) and the individual patient data from IST 1997 (Sandercock 2011). These sources reported that this population included primary ICH (52%) and haemorrhagic transformation of ischaemic stroke (48%), but unfortunately the chief investigator informed us that it would be impossible to isolate the participants with primary ICH (IST 1997). Frontera 2014 was excluded because it was not randomised. Li 2013 assessed transfusion of frozen apheresis platelets in patients with ICH and on aspirin. Venturelli 2014 was a post hoc analysis of a RCT in which antithrombotic treatment was not randomly assigned, making this analysis observational in nature. Yan 2014 included a population of patients with and without cerebral microbleeds after acute ischaemic stroke.

Risk of bias in included studies

We assessed risks of bias for both included RCTs (Dickmann 1988; Orken 2009). Please refer to Figure 2 and Figure 3 for graphical depictions of this analysis.

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

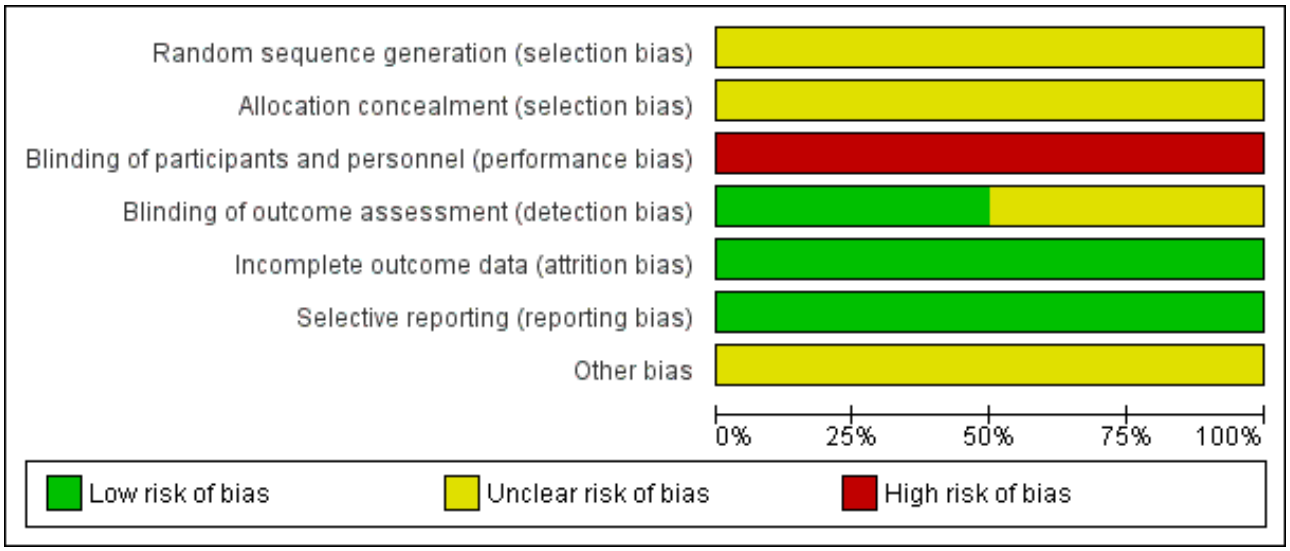
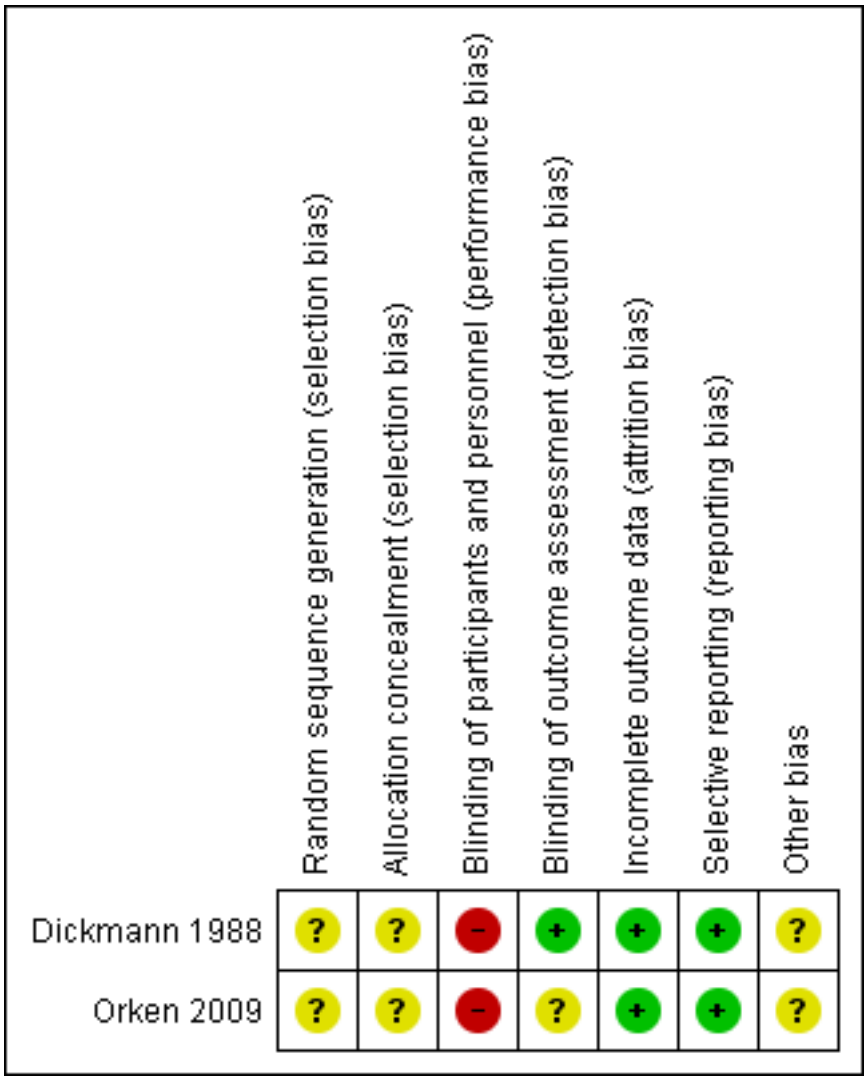


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Both Dickmann 1988 and Orken 2009 were reported to be randomised but neither RCT described the method of randomisation, and neither RCT described the method of allocation concealment. We therefore determined both RCTs to be at unclear risk of selection bias.

Blinding

Due to the nature of the intervention (subcutaneous injection), and lack of placebo, blinding of participants and the personnel delivering the intervention was not possible. Both Dickmann 1988 and Orken 2009 were therefore at high risk of performance bias.

Dickmann 1988 explicitly mentioned blinding of outcome raters and was at low risk of detection bias. Orken 2009 reported that radiologists were blinded to the clinical baseline radiological findings, but did not explicitly mention blinding of treatment allocation and was therefore at unclear risk of detection bias.

Incomplete outcome data

Outcome data were complete in both included RCTs, which were both rated at low risk of attrition bias.

Selective reporting

Both Dickmann 1988 and Orken 2009 reported all outcomes planned in their respective Methods sections, and each reported most expected outcomes of interest. Both included RCTs were therefore at low risk of reporting bias.

Other potential sources of bias

Neither Dickmann 1988 nor Orken 2009 described conflicts of interest or sources of funding. Neither study was prospectively registered. Both were therefore at an unclear risk of other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Antithrombotic treatment compared to no antithrombotic treatment for intracerebral haemorrhage

Short-term antithrombotic treatment

We included two RCTs for this comparison (Dickmann 1988; Orken 2009). We were able to extract numerical data on some of the relevant outcomes.

Composite outcome of all serious vascular events

We were unable to calculate the composite vascular endpoint for either Dickmann 1988 or Orken 2009 (Analysis 1.1).

Death

Only one RCT reported death from all causes (Dickmann 1988). The causes of death in this RCT were rebleeding (4), bronchopneumonia (4), and heart failure (1). There was no statistically significant difference between the intervention and control groups for this outcome (risk ratio (RR) 1.25, 95% confidence interval (CI) 0.38 to 4.07; Analysis 1.2; 46 participants).

Vascular death

Only one RCT reported deaths, but it did not adequately report in which group (control/intervention) instances of death from bronchopneumonia (4) and heart failure (1) occurred (Dickmann 1988). Because death from heart failure constitutes a vascular death and it was unclear in which group this death occurred, we were unable to include data for this outcome. However, it was reported that three deaths from expansion of the haematoma occurred in the control group and one such death occurred in the intervention group.

Ischaemic stroke

This outcome was not reported by either Dickmann 1988 or Orken 2009.

Myocardial infarction

This outcome was not reported by either Dickmann 1988 or Orken 2009.

Other major ischaemic event

Both included RCTs reported other major ischaemic events (Dickmann 1988; Orken 2009). All events for this outcome were pulmonary embolism detected by CT pulmonary angiogram (Orken 2009) or lung perfusion scintigraphy (Dickmann 1988). We combined results in a meta-analysis (Analysis 1.6), and detected no statistically significant difference between groups (RR 0.54, 95% CI 0.23 to 1.28; 121 participants). The results of this analysis are limited by the different methods of detecting pulmonary emboli used by each study group.

Intracerebral haemorrhage

One RCT involving 75 participants reported this outcome (Orken 2009). There were no recorded events in either group.

Major extracerebral haemorrhage

One RCT involving 75 participants reported this outcome (Orken 2009). There were no recorded events in either group.

Growth of ICH

Both of the included studies reported on ICH growth. Dickmann 1988 had an ambiguous definition for this outcome, 'rebleeding', which we considered to refer to ICH growth (whether this was due to continued bleeding, or recurrent ICH after cessation of the first ICH). This study did not describe a threshold of increased volume above which ICH growth was deemed to occur, and conducted brain CTs on days 1, 6, and 10 after ICH. Orken 2009 defined ICH growth as an increase in volume on CT of more than 33% or more than 12.5 mL using the ABC/2 method (Kothari 1996), and checked for this outcome on follow-up brain CTs at 24 hours, 72 hours, day 7, and day 21 after ICH. We combined the results from these two RCTs in a meta-analysis (Analysis 1.9), and observed no statistically significant differences between groups (RR 1.64, 95% CI 0.51 to 5.29; 121 participants).

Deep vein thrombosis

Both included studies reported on the outcome of deep vein thrombosis (DVT). All events for this outcome were DVT detected by phleboscintigraphy at days 2 and 10 (Dickmann 1988) or by venous doppler ultrasound examination on day 7 (Orken 2009). All events reported in Orken 2009 were asymptomatic, whereas Dickmann 1988 did not specify whether events were symptomatic or not. We detected no statistically significant difference between groups for this outcome (RR 0.99, 95% CI 0.49 to 1.96; Analysis 1.10; 121 participants).

Functional status

This outcome was not reported by either Dickmann 1988 or Orken 2009.

Cognitive status

This outcome was not reported by either Dickmann 1988 or Orken 2009.

Long-term antithrombotic treatment

We did not find any completed RCTs that investigated long-term antithrombotic treatment.

DISCUSSION

Summary of main results

We found some evidence on the short-term effects of antithrombotic drugs after ICH in two RCTs (Dickmann 1988; Orken 2009), but no evidence on the effects of long-term antithrombotic treatment. We were unable to calculate the composite primary outcome of all serious vascular events due to incompleteness of reporting of the component outcomes in the included RCTs (Dickmann 1988; Orken 2009). None of the outcomes reported showed a statistically significant difference between groups, possibly because the two included RCTs were inadequately powered to detect significant differences for our outcomes. Neither included RCT reported outcomes for ischaemic stroke, myocardial infarction, functional status, or cognitive status. We were unable to extract data on any prespecified subgroups.

Overall completeness and applicability of evidence

The evidence available from completed RCTs of short-term antithrombotic drug treatment after ICH is sparse. Data from the two included RCTs contribute moderately applicable evidence to this field; their inclusion criteria and settings are representative of typical ICH patients. The applicability of Dickmann 1988 is somewhat limited by waiting to start treatment until after day four

following ICH onset; one implication might be that some of the potential effects of subcutaneous heparin, for example those on ICH growth, never manifested. There is no comparative evidence on the differences between distinct types of anticoagulants used in this setting. Dickmann 1988 investigated the effects of heparin, whereas Orken 2009 used enoxaparin sodium, a low-molecular-weight heparin.

However, we were encouraged to find that there are seven ongoing RCTs investigating long-term antithrombotic treatment after ICH (APACHE-AF; PICASSO; NASPAF-ICH; RESTART; RESTART Nord de France; SoSTART; STATICH).

Quality of the evidence

The methodological quality of the included RCTs was limited by randomisation and allocation concealment not being described, failure to blind participants, and the optimal information size criterion not being met. The overall quality of evidence was therefore low. Both studies, despite investigating different drugs and starting treatment at different times, found no statistically significant difference between groups for outcomes relevant to this review. It is possible that this is due to these RCTs being inadequately powered to detect statistically meaningful differences, rather than there being no effect of the interventions.

Potential biases in the review process

None identified.

Agreements and disagreements with other studies or reviews

We identified two systematic reviews on short-term antithrombotic treatment (Keir 2002; Paciaroni 2011). Keir 2002 included data from three RCTs (CAST 1997; Dickmann 1988; IST 1997) and included individual patient data from IST 1997 and CAST 1997 on participants with both primary ICH (52%) as well as haemorrhagic transformation of ischaemic infarcts (48%), but did not describe results for these groups separately. Keir 2002 preceded Orken 2009, a study which we included in this review. The second systematic review we identified included non-randomised controlled studies (Paciaroni 2011). The non-randomised studies included in this review were Wasay 2008 and Tetri 2008. This review concluded that early antithrombotic treatment was associated with a significant reduction in pulmonary embolism, a non-significant reduction in mortality, and a non-significant increase in haemorrhagic expansion (Paciaroni 2011). We identified one systematic review on long-term antithrombotic use after ICH, but it could not draw any conclusions from the two epidemiological studies and several case series that it included (Flynn 2010b).

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence from two RCTs of short-term parenteral anticoagulation after ICH neither support nor discourage the use of short-term antithrombotic treatment after ICH.

There are no published RCTs on long-term antithrombotic treatment after ICH, but seven RCTs are ongoing at the time of this review.

At the present time, clinicians will have to use other sources of information to support clinical judgements.

Implications for research

Research on the use of antithrombotic drugs after ICH represents an area of unmet need for patients, clinicians, and other consumers. These data suggest that further high-quality RCTs are needed. For short-term antithrombotic use, future studies should consider functional outcome and quality of life in addition to clinical outcomes, such as ischaemic events, haemorrhagic events, or death. For long-term antithrombotic use, future RCTs should consider investigating the relative effectiveness and safety of different antithrombotic drugs, for example warfarin, aspirin, and the direct oral anticoagulants.

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CHARACTERISTICS OF STUDIES

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

Dickmann 1988

Methods	RCT

Dickmann 1988 *(Continued)*

	Duration: 10 days Design: parallel Setting: inpatient unit in Germany Dates: not described
Participants	46 participants Diagnosis: intracerebral haemorrhage Diagnosis model: cranial CT Eligibility criteria: diagnosis of ICH in the previous 24 hours before admission Exclusion criteria: bleeding diathesis, diastolic blood pressure higher than 120 mmHg, and deep coma with clinical signs of brain herniation Age (years, mean (SD)): 62 (SD not described) (intervention group), 60 (SD not described) (control group) Sex: 52% female (intervention group), 48% female (control group)
Interventions	1. 5000 units of heparin administered subcutaneously 8-hourly starting at day 4 (n = 23) 2. 5000 units of heparin subcutaneously 8-hourly starting at day 10 (n = 23) Both groups had the same treatment otherwise, with compression stockings and physical treatment
Outcomes	Rebleeding occurring during the trial period Thrombosis of abdomen or legs at day 2 and day 10 Pulmonary embolism at day 10 Death during the trial period
Notes	Rebleeding is not defined by the authors of this study and could mean multiple things. Conflicts of interest and sources of funding were not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not possible due to the control group not receiving a placebo injection
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All scintigrams were read by the same blinded investigators"
Incomplete outcome data (attrition bias)	Low risk	Outcome data were complete

Dickmann 1988 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	All outcomes planned in the Methods section were reported in full in the Results section. Additionally, most expected outcomes of interest were reported in this study
Other bias	Unclear risk	To our knowledge this study was not prospectively registered

Orken 2009

Methods	RCT Duration: 21 days Design: parallel Setting: inpatient unit in Turkey Dates: between January 2006 and March 2008
Participants	75 participants Diagnosis: intracerebral haemorrhage Diagnosis model: cranial CT Eligibility criteria: diagnosis of primary ICH Exclusion criteria: early death before heparin treatment, death before 7th day investigations, secondary ICH due to aneurysm, arteriovenous malformations, traumas and tumours. Excessive anticoagulation (INR > 2.0). Contraindication to contrast agents Age (years, mean (SD)): 68.1 (11.98) (intervention group) 66.08 (9.55) (control group) Sex: 56% female (intervention group), 22% female (control group) Additonal details: mean National Institutes of Health Stroke Scale scores on admission for the LMWH group was 9.74 ± 6.06 and for the compression stocking group was 8.61 ± 6.87. 32/39 participants in the LMWH group and 29/36 participants in the compression stocking group had hypertension identified as a risk factor for ICH. 11 participants from the LMWH group and 6 from the compression stocking group had had a prior cerebrovascular accident
Interventions	1. Enoxaparin sodium 48 mg/day (n = 39) 2. Compression stocking control (n = 36) Treatment began after the first 48 hours from hospital admission
Outcomes	Haematoma enlargement at 72 hours, 7 days and 21 days. Haematoma enlargement was defined as an increase in volume of > 33% or 12.5 mL Systemic bleeding complications DVT or PE based on CTPA and bilateral venous Doppler at 7 days
Notes	Conflicts of interest and sources of funding were not described

Risk of bias

Bias	Authors' judgement	Support for judgement

Orken 2009 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	The method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible due to 1 group receiving a subcutaneous injection and the other group receiving compression stockings
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"All radiologic material was prospectively evaluated by 2 radiologists ... who were blinded to the clinical findings and cranial CTs of the patients". The methods did not explicitly state that the radiologists were also blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were complete
Selective reporting (reporting bias)	Low risk	All outcomes planned in the Methods section were reported in full in the Results section. Additionally, most expected outcomes of interest were reported in this study
Other bias	Unclear risk	To our knowledge this study was not prospectively registered

CT: computed tomography
CTPA: CT pulmonary angiography
DVT: deep vein thrombosis
ICH: intracerebral haemorrhage
INR: International normalised ratio
LMWH: low-molecular-weight heparin
PE: pulmonary embolism
RCT: randomised controlled trial
SD: standard deviation

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

Study	Reason for exclusion
Boeer 1991	This is an extension phase of Dickmann 1988 that introduces non-randomised data to the previously published data.
CAST 1997	This trial included some people with ICH who were randomised prior to CT. These data were not available in the original manuscript. We had hoped that there would be useable data published in the Keir 2002 systematic review, but this did not separate primary ICH from haemorrhagic transformations of acute ischaemic stroke and we were therefore unable to include data from CAST 1997 in this review.
Frontera 2014	This is a controlled clinical trial that was not randomised.
IST 1997	This trial included several hundred participants with ICH who were randomised prior to CT. These data were not available in the original manuscript. We had hoped that data from the Keir 2002 systematic review or the published individual data forms (Sandercock 2011) would yield useable data for this review, but Keir 2002 did not report primary ICH separately from haemorrhagic expansion

Study	Reason for exclusion
	of an acute ischaemic stroke, and after contacting the chief investigator of IST 1997 we discovered that it was not possible to extract data on primary ICH separately.
Li 2013	The intervention randomised in this study is transfusion of frozen apheresis platelets in participants on aspirin and with ICH.
Venturelli 2014	This is a post hoc analysis of the INTERACT2 trial. The intervention that is the subject of this analysis, prophylactic subcutaneous heparin after ICH, was not randomly assigned in INTERACT2. Therefore, this analysis is observational in nature.
Yan 2014	The participant group did not have primary ICH; it was a cohort of people with and without cerebral microbleeds and haemorrhagic transformation, with acute ischaemic stroke following rtPA treatment.

CT: computed tomography
ICH: intracerebral haemorrhage
rtPA: Recombinant tissue plasminogen activator

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

APACHE-AF

Trial name or title	Apixaban versus antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation (APACHE-AF)
Methods	Allocation: randomised Blinding: open-label (none) Duration: 12 to 30 months Setting: multicentre trial across the Netherlands Dates: September 2014 and currently recruiting
Participants	Inclusion criteria • ICH (including isolated spontaneous intraventricular haemorrhage), documented with CT or MRI, during treatment with anticoagulation (VKA, any direct thrombin inhibitor, any factor Xa inhibitor, or (low- molecular-weight) heparin at a therapeutic dose) • Haemorrhage occurred between 7 and 90 days before randomisation • Diagnosis of (paroxysmal) non-valvular AF, documented on electrocardiography • A CHA2DS2-VASc score ≥ 3 • Score on the mRS ≤ 4 • Equipoise regarding the optimal medical treatment for the prevention of stroke • Age ≥ 18 years • Written informed consent by the participant or by a legal representative Exclusion criteria • Conditions other than AF for which the participant requires long-term anticoagulation • A different clinical indication for the use of an antiplatelet drug even if treated with apixaban, such as clopidogrel for recent coronary stenting • Mechanical prosthetic heart valve (biological prosthetic heart valves are allowed) or rheumatic mitral valve disease • Serious bleeding event in the previous 6 months, except for ICH

APACHE-AF *(Continued)*

	• High risk of bleeding (e.g. active peptic ulcer disease, a platelet count of < 100,000 mL-1 or haemoglobin level of < 6.2 mMol.L-1, ischaemic stroke in the previous 7 days (participants are eligible thereafter), documented haemorrhagic tendencies, or blood dyscrasias) • Current alcohol or drug abuse • Life expectancy of < 1 year • Severe renal insufficiency (a serum creatinine level of more than 221 µmol per litre or a calculated creatinine clearance of < 15 ml per minute) • Alanine aminotransferase or aspartate aminotransferase level > 2 times the upper limit of the normal range or a total bilirubin > 1.5 times the upper limit of the normal range, unless a benign causative factor (e.g. Gilbert's syndrome) is known or identified • Allergy to apixaban • Use of strong cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) inhibitors (e.g. systemic azole-antimycotics as ketoconazole or HIV protease inhibitors such as ritonavir) • Pregnant or breastfeeding • Women of childbearing potential: any woman who has begun menstruation and is not postmenopausal or otherwise permanently unable to conceive. A postmenopausal woman is defined as a woman who is over the age of 45 and has not had a menstrual period for at least 12 months
Interventions	Participants will be randomised into 6 groups • apixaban • aspirin • carbasalate calcium • clopidogrel • dipyridamole • no antithrombotic treatment Each of the groups will run in parallel
Outcomes	Primary outcome measures • Number of participants who experience the combination of vascular death or non-fatal stroke (cerebral infarction, intracerebral haemorrhage, or subarachnoid haemorrhage) Secondary outcome measures: number of participants who experience: • vascular death • death from any cause • all stroke • ischaemic stroke • intracerebral haemorrhage • other major extracranial haemorrhage • any intracranial haemorrhage other than ICH • systemic embolism • myocardial infarction • a good functional outcome as assessed with the score on the mRS
Starting date	September 2014
Contact information	Contact: Koen M van Nieuwenhuizen, MD. Tel: +31 88 757 4097; email: k.m.vannieuwenhuizen-3@umcutrecht.nl Contact: H Bart van der Worp, MD PhD. Tel: +31 88 755 98 99; email: h.b.vanderworp@umcutrecht.nl
Notes	

NASPAF-ICH

Trial name or title	Non-VKA Anticoagulants for Stroke Prevention in Patients with Atrial Fibrillation and Previous IntraCerebral Hemorrhage Study (NASPAF-ICH)
Methods	Allocation: randomised 2:1 (non-vitamin K oral antagonist (agent at the discretion of the local investigator) vs aspirin) Blinding: open-label, blinded adjudication of outcomes Duration: recruitment 24 months, participants will be followed to a common terminate date designated at 6 months following the end of recruitment. Average follow-up per participant approximately 12 months (range: 12 to 30 months) Design (parallel, other): phase II, open-label randomised controlled trial Setting: 10 high-volume stroke centres across Canada Dates: January 2017 to June 2019
Participants	Inclusion criteria • 45 years of age or older • prior spontaneous intraparenchymal or intraventricular haemorrhage • High risk AF (CHADS2 ≥ 2) Exclusion criteria • Non-stroke indication for antiplatelet or anticoagulant therapy • Estimated creatinine clearance of < 30 ml per minute • Platelet count less than 100,000/mm^3 at enrolment or other bleeding diathesis • Uncontrollable hypertension with SBP/DBP consistently above 160/100 mmHg • Prior symptomatic lobar ICH other than the qualifying event (i.e. ≥ 2 symptomatic lobar ICH) • Known hypersensitivity to either aspirin or NOACs • Pregnant or breastfeeding
Interventions	Non-vitamin K oral antagonist (agent at the discretion of the local investigator) vs aspirin 81 mg Strict long-term blood pressure control to target of < 130/80 mmHg for all participants
Outcomes	Primary outcome measure: the primary feasibility outcome will be recruitment rates Secondary outcomes will be refusal rates and retention rates
Starting date	January 2017
Contact information	Co-Prinicipal Investigator: Ashkan Shoamanesh, MD, FRCPC Assistant Professor of Medicine (Neurology) Director, Stroke Fellowship Program Marta and Owen Boris Chair in Stroke Research and Care McMaster University / Population Health Research Institute 237 Barton Street East HGH-DBCVSRI C4-118 Hamilton, Ontario, L8L 2X2, Canada Email: ashkan.shoamanesh@phri.ca

NASPAF-ICH *(Continued)*

	Telephone: (905) 521-2100 ext 41277 Fax: (905) 577-1427
Notes	

PICASSO

Trial name or title	PreventIon of CArdiovascular Events in iSchemic Stroke patients with high risk of cerebral hemOrrhage (PICASSO)
Methods	Allocation: randomisation Blinding: double-blinding (participant, caregiver, investigator, outcome assessor) Duration: 1 to 5.5 years Setting: multicentre trial across China, South Korea and the Philippines Dates: June 2009 and ongoing
Participants	Inclusion criteria • People with TIA or ischaemic stroke within 180 days prior to screening - adult aged 20 years or older • High risk of haemorrhagic stroke (history of intracranial haemorrhage or imaging evidence of previous intracranial haemorrhage) • Informed consent Exclusion criteria • Clinical diagnosis of myocardial infarction or coronary intervention within 4 weeks • Bleeding tendency • Pregnant or breastfeeding woman • Haemorrhagic stroke within 6 months • Person taking antithrombotic medication other than aspirin and not agreeing to change the previous medication • Severe cardiovascular disease such as cardiomyopathy or congestive heart failure • Life expectancy < 1 year • Contraindication to long-term aspirin use • Enrolled in other clinical trial within 30 days
Interventions	A factorial design across the following groups: • cilostazol • probucol • aspirin • placebo of cilostazol • placebo of aspirin
Outcomes	Primary outcome measures: time to first occurrence of: • cerebral haemorrhage • composite cardiovascular events Secondary outcome measures: time to first occurrence of:

PICASSO *(Continued)*

	• stroke • ischaemic stroke • myocardial infarction • other designated vascular events Other outcome measures • Incidence rate of major and non-major haemorrhagic event • Rate of asymptomatic haemorrhage in GRE (microhaemorrhage or macrohaemorrhage) • Rate of new asymptomatic cerebral infarction lesion in FLAIR • Change of ankle-brachial index • The effect of the size of CCA including plaque on the occurrence of cardiovascular events • Time to all deaths including vascular and non-vascular death • Incidence rate of dementia diagnosed after initiation of the trial
Starting date	June 2009
Contact information	Principal Investigator: Sun U Kwon, MD, PhD Departement of Neurology, Asan Medical Center
Notes	

RESTART

Trial name or title	REstart or STop Antithrombotics Randomised Trial (RESTART)
Methods	Allocation: randomised Blinding: treatment is open-label, but outcome assessors are blinded Duration: at least 6 months Design: parallel Setting: UK National Health Service (NHS) secondary care (inpatient and outpatient services in stroke, neurology and neurosurgery) and primary care Dates: May 2013 to May 2018 (recruitment), November 2018
Participants	Inclusion criteria: • Patient age ≥ 18 years. • Spontaneous primary or secondary ICH. • Patient had taken antithrombotic drug(s) for the prevention of vaso-occlusive disease before ICH onset. Randomisation > 24 hours after ICH onset. • Patient and their doctor are uncertain about whether to start or avoid antiplatelet drugs. • Patient is registered with a general practitioner (GP). • Brain imaging that first diagnosed the ICH is available. • Participant or representative consent. Exclusion criteria: • ICH due to preceding trauma or haemorrhagic transformation of ischaemic stroke. • Patient is taking an anticoagulant drug following ICH. • Patient is pregnant, breastfeeding, or of childbearing age and not taking contraception. • Patient is being treated or followed up in another CTIMP.

RESTART *(Continued)*

	• Patient and carer unable to understand spoken or written English. Brain magnetic resonance imaging (MRI) sub-study: MRI done after ICH but before randomisation. No claustrophobia. MRI not contraindicated
Interventions	Participants will be randomised to either 'start antiplatelet medication' (restricted to the use of 1 or more of aspirin, dipyridamole or clopidogrel at the investigator's discretion) or "avoid antiplatelet medication"
Outcomes	Primary outcome measure: recurrent symptomatic ICH Secondary outcome measures: • possible recurrent ICH; • symptomatic non-fatal extracerebral haemorrhage, extracranial haemorrhage, and vaso-occlusive events; death; • modified Rankin Scale score; • adherence to antiplatelet drug(s)
Starting date	April 2013
Contact information	UK Chief Investigator: Rustam Al-Shahi Salman; Trial Manager: Karen Innes RESTART.trial@ed.ac.uk.
Notes	

RESTART Nord de France

Trial name or title	RESTART Nord de France
Methods	Allocation: randomisation 1:1 - restart vs no antiplatelet Blinding: PROBE design Duration: each participant will be followed up during year 2 Design (parallel, other): RCT 1:1 Setting: region North of France Dates: start October 2016, recruitment 3 years, overall: 5 years
Participants	Inclusion criteria • Adult, no upper age limit • Spontaneous ICH • Randomisation at least 24 hours following the index ICH • The participant and the doctor are uncertain about the net clinical benefit of restarting or not antiplatelet agents Exclusion criteria • Traumatic ICH • Secondary ICH • MRI contra-indications
Interventions	Restart antiplatelet agent vs no antiplatelet agent

RESTART Nord de France *(Continued)*

Outcomes	Primary outcome measure: recurrent ICH (fatal and non fatal) Secondary outcome measures: • Serious vascular events fatal (followed by death within 30 days) and non-fatal • Symptomatic haemorrhagic events (excluding cerebrovascular) • Symptomatic ischaemic events (cerebral and extracerebral) • Stroke of undetermined nature • Other fatal events • Functional outcome at 2 years • Incident brain microhaemorrhages on follow-up MRI at 1 year
Starting date	October 2016
Contact information	Contact information: Professor Charlotte Cordonnier charlotte.cordonnier@chru-lille.fr
Notes	

SoSTART

Trial name or title	Start or STop Anticoagulants Randomised Trial
Methods	Investigator-led, multicentre, randomised, open, assessor-masked, parallel group, clinical trial of investigational medicinal product (CTIMP) prescribing strategies. We plan for a pilot phase, followed by a main phase.
Participants	Inclusion criteria: spontaneous intracranial haemorrhage, AF and a CHA_2DS_2-VASc score ≥ 2 Exclusion criteria: • Patient age < 18 years • Intracranial haemorrhage within the last 24 hours • Brain imaging that first diagnosed the intracranial haemorrhage is not available • Intracranial haemorrhage is exclusively due to trauma or haemorrhagic transformation of ischaemic stroke. Patient or their doctor is certain about whether to start or avoid full oral anticoagulation • Patient is not registered with a general practitioner • Patient is pregnant, breastfeeding, or of childbearing age and not taking contraception • Patient and carer unable to understand spoken or written English • Previously randomised in SoSTART Brain MRI substudy: MRI must be done after intracranial haemorrhage but before randomisation. Substudy participants must not have contraindications to MRI.
Interventions	• Start full OAC: (either a non-vitamin K antagonist DOAC or warfarin if a DOAC cannot be used), chosen by the participant's physician before randomisation • Start antiplatelet drug(s) (if the participant has an indication for antiplatelet drugs) or avoid all antithrombotic drugs (if the participant does not have an indication for antiplatelet drugs), specified by the participant's doctor before randomisation
Outcomes	Primary outcome: all symptomatic serious vascular events (i.e. major adverse cardiac or cerebrovascular events: MACCE) including non-fatal stroke, non-fatal acute coronary syndrome, vascular death, sudden death, or death of unknown cause

SoSTART *(Continued)*

	Secondary outcomes: • individual symptomatic vascular events; • individual types of fatal events; • dependence according to the mRS
Starting date	2017
Contact information	Professor Rustam Al-Shahi Salman, University of Edinburgh, UK (Rustam.Al-Shahi@ed.ac.uk)
Notes	Funded by Chest Heart and Stroke Scotland

STATICH

Trial name or title	Study of Antithrombotic Treatment after Intracerebral Haemorrhage (STATICH)
Methods	Allocation: randomised Blinding: open, blinded endpoint Duration: 2 years Design : parallel Setting: multicenter in Norway, Denmark, and Sweden Dates: start up 2017
Participants	Inclusion criteria: • Spontaneous, primary ICH • No preceding traumatic injury, no structural secondary underlying structural cause • Indication for antithrombotic drug • Uncertainty about whether to start or avoid antithrombotic drugs after ICH • Patient age ≥ 18 years • Patient is at least 24 hours after symptom onset • Consent from patient or representative Exclusion criteria: • Absolute indication for anticoagulant treatment • Patient is pregnant, breastfeeding or of childbearing age and not taking contraception • Patient is being treated or followed up in another CTIMP For MRI substudy: contraindication for MRI
Interventions	Interventions for each group: the intervention is starting antithrombotic drug. The comparator is avoiding antithrombotic drugs
Outcomes	Primary outcome measure: recurrent symptomatic ICH Secondary outcome measures: • complication of qualifying ICH; • symptomatic extradural haemorrhage, subdural haemorrhage, subarachnoid haemorrhage; • symptomatic major extracranial haemorrhage; • symptomatic ischaemic events;

STATICH *(Continued)*

	• cardiovascular death; death from any other cause; • mRS
Starting date	
Contact information	Trial co-ordinating investigator: Eivind Berge, MD, PhD, email: eivind.berge@medisin.uio.no Trial manager: Elisabeth Forfang, MD, email: elisabeth.forfang@medisin.uio.no
Notes	

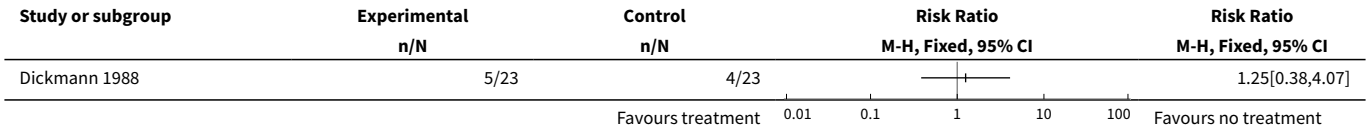
AF: atrial fibrillation
CCA: common carotid artery
CT: computed tomography
DBP: diastolic blood pressure
DOAC: direct oral anticoagulant
ICH: intracerebral haemorrhage
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NOAC: novel oral anticoagulant
OAC: oral anticoagulation
SBP: systolic blood pressure
TIA: transient ischaemic stroke
VKA: vitamin K antagonist

DATA AND ANALYSES

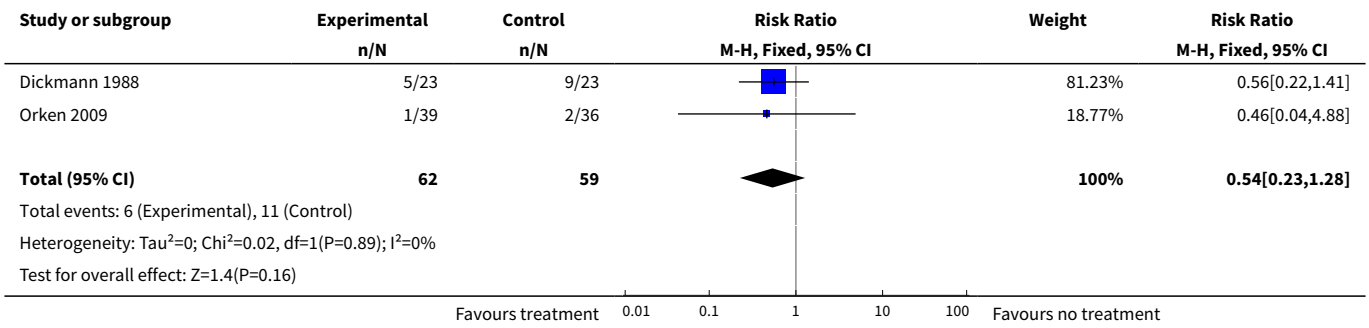
Comparison 1. Short-term antithrombotic treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Other major ischaemic event	2	121	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.23, 1.28]
7 Intracerebral haemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Major extracerebral haemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Growth of intracerebral haematoma	2	121	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.51, 5.29]
10 Deep vein thrombosis	2	121	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.49, 1.96]

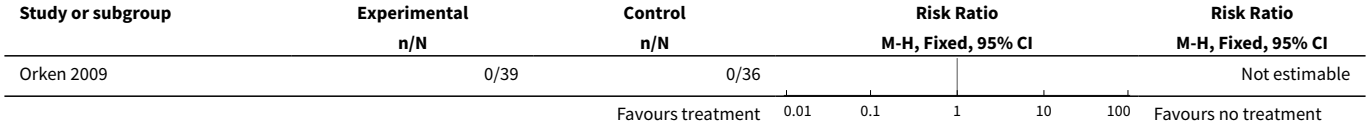
Analysis 1.2. Comparison 1 Short-term antithrombotic treatment, Outcome 2 Death.



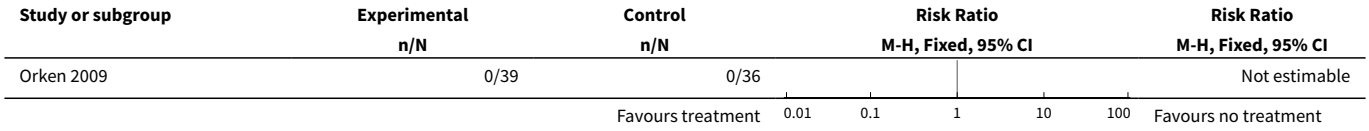
Analysis 1.6. Comparison 1 Short-term antithrombotic treatment, Outcome 6 Other major ischaemic event.



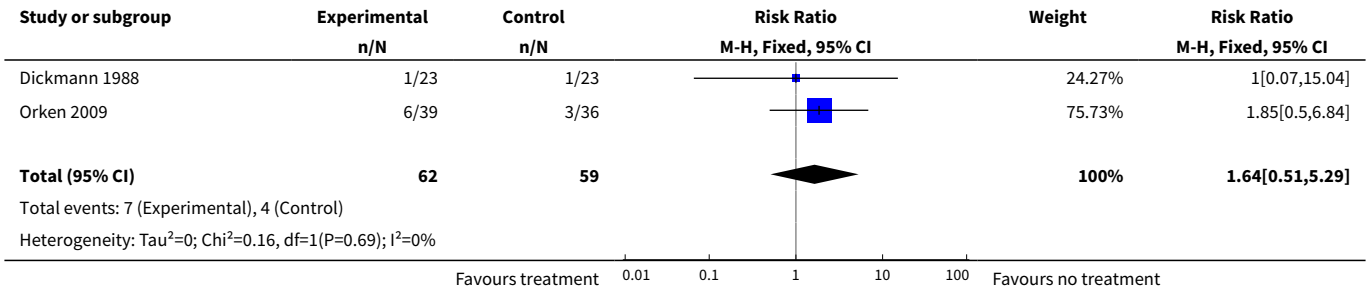
Analysis 1.7. Comparison 1 Short-term antithrombotic treatment, Outcome 7 Intracerebral haemorrhage.

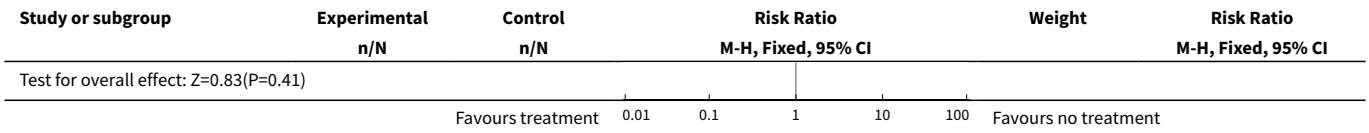


Analysis 1.8. Comparison 1 Short-term antithrombotic treatment, Outcome 8 Major extracerebral haemorrhage.

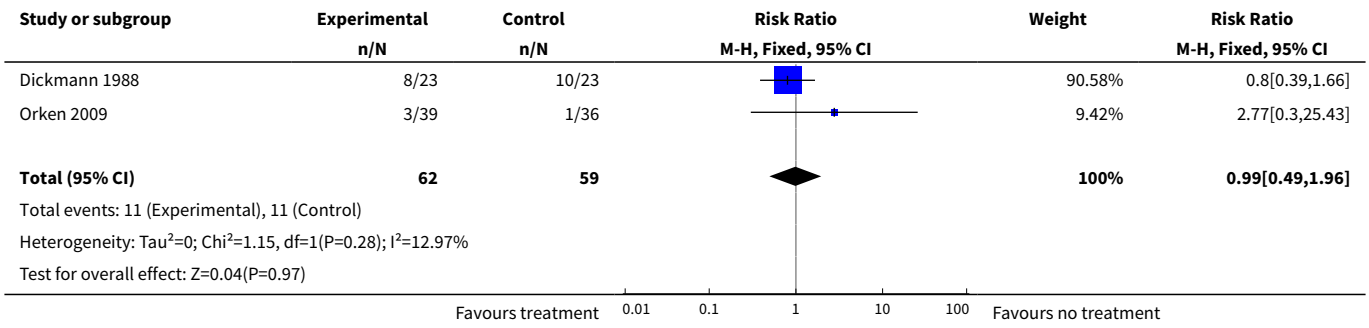


Analysis 1.9. Comparison 1 Short-term antithrombotic treatment, Outcome 9 Growth of intracerebral haematoma.





Analysis 1.10. Comparison 1 Short-term antithrombotic treatment, Outcome 10 Deep vein thrombosis.



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MESH DESCRIPTOR Basal Ganglia Hemorrhage EXPLODE ALL TREES

#2 MESH DESCRIPTOR Intracranial Hemorrhages

#3 MESH DESCRIPTOR Intracranial Hemorrhage, Hypertensive

#4 MESH DESCRIPTOR Cerebral Hemorrhage

#5 (brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or putaminal or putamen or hemispher* or stroke or apoplex*):TI

#6 (basal and gangli*):TI

#7 (posterior and fossa):TI,AB,KY

#8 (haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed*):TI

#9 #5 or #6 or #7 and #8

#10 (ICH or ICHs):TI

#11 #1 or #2 or #3 or #4 or #9 or #10

#12 MESH DESCRIPTOR Anticoagulants EXPLODE ALL TREES

#13 MESH DESCRIPTOR Pipecolic Acids EXPLODE ALL TREES WITH QUALIFIERS AE,TU

#14 MESH DESCRIPTOR Vitamin K EXPLODE ALL TREES

#15 MESH DESCRIPTOR Thrombin EXPLODE ALL TREES WITH QUALIFIERS AI

#16 MESH DESCRIPTOR Factor Xa

#17 MESH DESCRIPTOR Blood Coagulation Factors EXPLODE ALL TREES WITH QUALIFIERS AI

#18 MESH DESCRIPTOR Blood Coagulation EXPLODE ALL TREES WITH QUALIFIERS DE

#19 MESH DESCRIPTOR Antithrombins EXPLODE ALL TREES

#20 MESH DESCRIPTOR Hirudin Therapy EXPLODE ALL TREES

#21 (anticoagul* or antithromb*):TI,AB,KY

#22 (Vitamin next K next antagonist*):TI,AB,KY

#23 (VKA or VKAs):TI,AB,KY

#24 #22 or #23

#25 (direct* NEAR5 thrombin):TI,AB,KY

#26 "DTI":TI,AB,KY

#27 (factor next Xa NEAR5 inhib*):TI,AB,KY

#28 (factor next 10a NEAR5 inhib*):TI,AB,KY

#29 (fXa NEAR5 inhib*):TI,AB,KY

#30 (autoprothrombin NEAR5 inhib*):TI,AB,KY

#31 (thrombokinase NEAR5 inhib*):TI,AB,KY

#32 (acenocoumarol* or dicoumarol* or ethyl next biscoumacetate* or phenprocoumon* or warfarin* or ancrod* or citric next acid* or coumarin* or chromonar* or coumestro* or esculi* or ochratoxin* or umbelliferone* or dermatan next sulfate* or dextran* or edetic next acid* or enoxaparin* or gabexate* or heparin* or lmwh* or nadroparin* or pentosan next sulfuric next polyester* or phenindione* or protein next c or protein next s or tedelparin*):TI,AB,KY

#33 (tinzaparin or parnaparin or dalteparin or reviparin or danaparoid or lomoparan or org next 10172 or mesoglycan or polysaccharide next sulphate* or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216):TI,AB,KY

#34 (Marevan or Fragmin* or Fraxiparin* or Klexane):TI,AB,KY

#35 (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin* or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil):TI,AB,KY

#36 (xabans or antistasin or apixaban or betrixaban or du next 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym next 150 or

ym150 or LY517717):TI,AB,KY

#37 #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36

#38 MESH DESCRIPTOR Platelet Glycoprotein GPIIb-IIIa Complex EXPLODE ALL TREES WITH QUALIFIERS AI,DE

#39 MESH DESCRIPTOR Platelet Activation EXPLODE ALL TREES WITH QUALIFIERS DE

#40 MESH DESCRIPTOR Blood Platelets EXPLODE ALL TREES WITH QUALIFIERS DE

#41 (antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg* or (platelet* NEAR5 inhibit*)

or (thrombocyt* NEAR5 inhibit*)):TI,AB,KY

#42 (alprostadil* or aspirin* or acetylsalicylic next acid or (acetyl ADJ salicylic and acid*) or

(acetyl-salicylic and acid or epoprostenol* or ketanserin* or ketorolac next tromethamine* or

milrinone* or mopidamol* or procainamide* or thiophen* or trapidil* or picotamide* or

ligustrazine* or levamisol* or suloctidil* or ozagrel* or oky046 or oky-046 or defibrotide* or

cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-

4151)):TI,AB,KY

#43 ((glycoprotein next iib* near/5 inhib*) or (glycoprotein next iib* near/5 antag*) or (gp next

iib* near/5 inhib*) or (gp next iib* near/5 antag*) or GR144053 or GR-144053 or triflusal):TI,AB,KY

#44 (Argatroban or Beraprost or Cicaprost or Cilostazol or Clopidogrel or Dipyridamole or

Iloprost or Indobufen or Lepirudin or Pentosan next Polysulfate or Pentoxifylline or Piracetam or

Prostacyclin or Sulfinpyrazone or Sulphinpyrazone or Ticlopidine or Triflusal or Abciximab or

Disintegrin or Echistatin or Eptifibatide or Lamifiban or Orbofiban or Roxifiban or Sibrafiban or

Tirofiban or Xemilofiban or terutroban or picotamide or prasugrel):TI,AB,KY

#45 (Dispril or Albyl* or Ticlid* or Persantin* or Plavix or ReoPro or Integrilin* or Aggrastat):TI,AB,KY

#46 MESH DESCRIPTOR Platelet Aggregation Inhibitors EXPLODE ALL TREES

#47 #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46

#48 #37 or #47

#49 #48 and #11

Appendix 2. MEDLINE search strategy

1. exp basal ganglia haemorrhage/ or intracranial hemorrhages/ or cerebral haemorrhage/ or intracranial haemorrhage, hypertensive/

2. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$) adj5 (h?emorrhag$ or h?ematoma$ or bleed $)).tw.

3. ((h?emorrhag$ or bleed$) adj5 (stroke or apoplex$)).tw.

4. (ICH or ICHs).tw.

5. 1 or 2 or 3 or 4

6. exp anticoagulants/

7. exp Vitamin K/ai or thrombin/ai or factor Xa/ai or exp Blood coagulation factors/ai

8. exp antithrombins/ or hirudin therapy/

9. (anticoagul$ or antithromb$).tw.

10. (Vitamin K antagonist$ or VKA or VKAs).tw.

11. (direct$ adj3 thrombin adj3 inhib$).tw.

12. DTI$1.tw.

13. ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj3 inhib$).tw.

14. (activated adj3 (factor X or factor 10) adj3 inhib$).tw.

15. (acenocoumarol$ or dicoumarol$ or ethyl biscoumacetate$ or phenprocoumon$ or warfarin$ or ancrod$ or citric acid$ or coumarin$ or chromonar$ or coumestro$ or esculi$ or ochratoxin$ or umbelliferone$ or dermatan sulfate$ or dextran$ or edetic acid$ or enoxaparin$ or gabexate$ or heparin$ or lmwh$ or nadroparin$ or pentosan sulfuric polyester$ or phenindione$ or protein c or protein s or tedelparin $).tw,nm.

16. (tinzaparin or parnaparin or dalteparin or reviparin or danaparoid or lomoparan or org 10172 or mesoglycan or polysaccharide sulphate $ or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216).tw,nm.

17. (Marevan or Fragmin$ or Fraxiparin$ or Klexane).tw,nm.

18. (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin$ or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil).tw,nm.

19. (xabans or antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717).tw,nm.

20. exp platelet aggregation inhibitors/ or exp platelet glycoprotein gpiib-iiia complex/ai

21. (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj3 inhibit$) or (thrombocyt$ adj3 inhibit$)).tw.

22. (alprostadil$ or aspirin$ or acetylsalicylic acid or acetyl salicylic acid$ or acetyl?salicylic acid or epoprostenol$ or ketanserin$ or ketorolac tromethamine$ or milrinone$ or mopidamol$ or procainamide$ or thiophen$ or trapidil$ or picotamide$ or ligustrazine$ or levamisol$ or suloctidil$ or ozagrel$ or oky046 or oky-046 or defibrotide$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or ((glycoprotein iib$ or gp iib$) adj5 (antagonist$ or inhibitor$)) or GR144053 or GR-144053 or triflusal).tw,nm.

23. (Beraprost or Cicaprost or Cilostazol or Clopidogrel or Dipyridamole or Iloprost or Indobufen or Lepirudin or Pentosan Polysulfate or Pentoxifylline or Piracetam or Prostacyclin or Sulfinpyrazone or Sulphinpyrazone or Ticlopidine or Triflusal or Abciximab or Disintegrin or Echistatin or Eptifibatide or Lamifiban or Orbofiban or Roxifiban or Sibrafiban or Tirofiban or Xemilofiban or terutroban or picotamide or prasugrel).tw,nm.

24. (Dispril or Albyl$ or Ticlid$ or Persantin$ or Plavix or ReoPro or Integrilin$ or Aggrastat).tw,nm.

25. or/6-24

26. Randomized Controlled Trials as Topic/

27. random allocation/

28. Controlled Clinical Trials as Topic/

29. control groups/

30. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/

31. double-blind method/

32. single-blind method/

33. Placebos/

34. placebo effect/

35. randomised controlled trial.pt.

36. controlled clinical trial.pt.

37. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.

38. (random$ or RCT or RCTs).tw.

39. (controlled adj5 (trial$ or stud$)).tw.

40. (clinical$ adj5 trial$).tw.

41. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

42. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

43. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.

44. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

45. (placebo$ or sham).tw.

46. trial.ti.

47. (assign$ or allocat$).tw.

48. or/26-47

49. 5 and 25 and 48

50. exp animals/ not humans/

51. 49 not 50

Appendix 3. EMBASE (Ovid) search strategy

1. anticoagulant agent/ or antivitamin k/ or exp blood clotting inhibitor/ or exp coumarin anticoagulant/ or defibrotide/ or dextran sulfate/ or fluindione/ or

glycosaminoglycan polysulfate/ or exp heparin derivative/ or lupus anticoagulant/ or phenindione/

2. (anticoagul$ or antithromb$).tw.

3. (Vitamin K antagonist$ or VKA or VKAs).tw.

4. (direct$ adj5 thrombin adj5 inhib$).tw.

5. DTI$1.tw.

6. ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj5

inhib$).tw.

7. (activated adj5 (factor X or factor 10) adj5 inhib$).tw.

8. (acenocoumarol$ or dicoumarol$ or ethyl biscoumacetate$ or phenprocoumon$ or

warfarin$ or ancrod$ or citric acid$ or coumarin$ or chromonar$ or coumestro$ or

esculi$ or ochratoxin$ or umbelliferone$ or dermatan sulfate$ or dextran$ or edetic acid$ or enoxaparin$ or gabexate$ or heparin$ or lmwh$ or nadroparin$ or pentosan sulfuric polyester$ or phenindione$ or protein c or protein s or tedelparin$).tw.

9. (tinzaparin or parnaparin or dalteparin or reviparin or danaparoid or lomoparan or org 10172 or mesoglycan or polysaccharide sulphate$ or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216).tw.

10. (Marevan or Fragmin$ or Fraxiparin$ or Klexane).tw.

11. (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin$ or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil).tw.

12. (xabans or antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717).tw.

13. or/1-12

14. exp antithrombocytic agent/

15. fibrinogen receptor/dt [Drug Therapy]

16. (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj5 inhibit$) or (thrombocyt$ adj5 inhibit$)).tw.

17. (alprostadil$ or aspirin$ or acetylsalicylic acid or acetyl salicylic acid$ or acetyl?salicylic acid or epoprostenol$ or ketanserin$ or ketorolac tromethamine$ or milrinone$ or mopidamol$ or procainamide$ or thiophen$ or trapidil$ or picotamide$ or ligustrazine$ or levamisol$ or suloctidil$ or ozagrel$ or oky046 or oky-046 or defibrotide$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or ((glycoprotein iib$ or gp iib$) adj5 (antagonist$ or inhibitor$)) or GR144053 or GR-144053 or triflusal).tw.

18. (Argatroban or Beraprost or Cicaprost or Cilostazol or Clopidogrel or Dipyridamole or Iloprost or Indobufen or Lepirudin or Pentosan Polysulfate or Pentoxifylline or Piracetam or Prostacyclin or Sulfinpyrazone or Sulphinpyrazone or Ticlopidine or Triflusal or Abciximab or Disintegrin or Echistatin or Eptifibatide or Lamifiban or Orbofiban or Roxifiban or Sibrafiban or Tirofiban or Xemilofiban or

terutroban or picotamide or prasugrel).tw.

19. (Dispril or Albyl$ or Ticlid$ or Persantin$ or Plavix or ReoPro or Integrilin$ or Aggrastat).tw.

20. or/14-19

21. 13 or 20

22. *basal ganglion hemorrhage/ or *brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/

23. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or stroke or apoplex$) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).ti.

24. 22 or 23 or (ICH or ICHs).ti.

25. randomized controlled trial/ or "randomized controlled trial (topic)"/

26. Randomization/

27. Controlled Study/

28. control group/

29. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/

30. Double Blind Procedure/

31. Single Blind Procedure/ or triple blind procedure/

32. placebo/

33. drug comparison/ or drug dose comparison/

34. "types of study"/

35. random$.tw.

36. (controlled adj5 (trial$ or stud$)).tw.

37. (clinical$ adj5 trial$).tw.

38. ((control or treatment or experiment$ or intervention or surgical) adj5 (group$ or subject$ or patient$)).tw.

39. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

40. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

41. placebo$.tw.

42. controls.tw.

43. or/25-42

44. meta analysis/ or "meta analysis (topic)"/ or "systematic review"/ or "systematic review (topic)"/

45. meta analy$.tw.

46. metaanaly$.tw.

47. (systematic adj (review$1 or overview$1)).tw.

48. literature/

49. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or medline or pubmed).ab.

50. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search).ab.

51. (selection criteria or data extraction).ab.

52. review.pt. or literature/ or review/

53. 51 and 52

54. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 53

55. (letter or editorial).pt.

56. 54 not 55

57. 43 or 56

58. 21 and 24 and 57

59. limit 58 to human

Appendix 4. Trials register search strategies

1. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov)

'Randomised' AND 'intracerebral haemorrhage'

2. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch)

'Intracerebral haemorrhage' OR 'Intracerebral hemorrhage' OR 'ICH'

3. ISRCTN Registry (www.isrctn.com)

'Intracerebral haemorrhage' OR 'Intracerebral hemorrhage' OR 'ICH'

4. Stroke Trials Registry – the Internet Stroke Center (www.strokecenter.org/trials/)

'Intracerebral haemorrhage' OR 'Intracerebral hemorrhage' OR 'ICH'

CONTRIBUTIONS OF AUTHORS

All authors, Luke A Perry, Eivind Berge, Joshua Bowditch, Elisabeth Forfang, Ole Morten Rønning, Graeme J Hankey, Elmer Villanueva, Rustam Al-Shahi Salman, contributed to planning, writing, and editing the review.

DECLARATIONS OF INTEREST

Luke A Perry: none known
Eivind Berge: co-ordinating investigator of the ongoing STATICH trial.
Joshua Bowditch: none known
Elisabeth Forfang: managing investigator of the ongoing STATICH trial.
Ole Morten Rønning: none known
Graeme J Hankey: in the past three years, GJH has received honoraria from AC Immune for chairing the data safety monitoring committee of two clinical trials of vaccines for Alzheimer's disease, from Bayer for lecturing about stroke prevention in atrial fibrillation at sponsored scientific symposia, and from Medscape, Web MD for participating in a discussion about stroke prevention in atrial fibrillation for theheart.org.
Elmer Villanueva: none known
Rustam Al-Shahi Salman: Chief investigator of the UK REstart or STop Antithrombotics Randomised Trial (RESTART, www.RESTARTtrial.org, ISRCTN71907627), which is funded by a special project grant from the British Heart Foundation.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We separately grouped RCTs investigating short-term and long-term treatment, instead of performing subgroup analyses as our protocol had specified.

We added two new outcomes: deep vein thrombosis and ICH growth, as we believe that they are of potential interest to consumers of this review. The addition of the outcome deep vein thrombosis allowed us to include it as a secondary outcome in this review without including it in another category (e.g. major ischaemic events). The addition of the ICH growth outcome is relevant to short-term antithrombotic treatment and was considered after we decided to divide our analysis into two groups according to the duration of antithrombotic drug use. The addition of these new outcomes did not result in any additional RCTs being included in this review.

We optimised the 'Summary of findings' tables to better reflect the outcomes of interest related to short- and long-term treatment.

INDEX TERMS

Medical Subject Headings (MeSH)

Cerebral Hemorrhage [*complications] [mortality]; Enoxaparin [*therapeutic use]; Fibrinolytic Agents [*therapeutic use]; Heparin [*therapeutic use]; Intracranial Thrombosis [*prevention & control]; Randomized Controlled Trials as Topic; Stroke [*drug therapy] [etiology]; Venous Thrombosis [epidemiology]

MeSH check words

Humans