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Heparin versus placebo for non-ST elevation acute coronary syndromes (Review)

Andrade-Castellanos CA, Colunga-Lozano LE, Delgado-Figueroa N, Magee K

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[Intervention Review]

Heparin versus placebo for non-ST elevation acute coronary syndromes

Carlos A Andrade-Castellanos[1], Luis Enrique Colunga-Lozano[2], Netzahualpilli Delgado-Figueroa[3], Kirk Magee[4]

[1]Department of Emergency Medicine, Hospital Civil de Guadalajara "Dr. Juan I. Menchaca", Guadalajara, Mexico. [2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada. [3]Department of Pediatrics, Hospital Civil de Guadalajara Dr. Juan I. Menchaca, Guadalajara, Mexico. [4]Department of Emergency Medicine, Dalhousie University, Halifax, Canada

Contact: Carlos A Andrade-Castellanos, caandrade@hcg.gob.mx.

A B S T R A C T

Background

Non-ST elevation acute coronary syndromes (NSTEACS) represent a spectrum of disease including unstable angina and non-ST segment myocardial infarction (NSTEMI). Despite treatment with aspirin, beta-blockers and nitroglycerin, unstable angina/NSTEMI is still associated with significant morbidity and mortality. Although evidence suggests that low molecular weight heparin (LMWH) is more efficacious compared to unfractionated heparin (UFH), there is limited data to support the role of heparins as a drug class in the treatment of NSTEACS. This is an update of a review last published in 2008.

Objectives

To determine the effect of heparins (UFH and LMWH) compared with placebo for the treatment of patients with non-ST elevation acute coronary syndromes (unstable angina or NSTEMI).

Search methods

For this update the Cochrane Heart Group Trials Search Co-ordinator searched the Cochrane Central Register of Controlled Trials on *The Cochrane Library* (2013, Issue 12), MEDLINE (OVID, 1946 to January week 1 2014), EMBASE (OVID, 1947 to 2014 week 02), CINAHL (1937 to 15 January 2014) and LILACS (1982 to 15 January 2014). We applied no language restrictions.

Selection criteria

Randomized controlled trials of parenteral UFH or LMWH versus placebo in people with non-ST elevation acute coronary syndromes (unstable angina or NSTEMI).

Data collection and analysis

Two review authors independently assessed quality of studies and independently extracted data.

Main results

There were no new included studies for this update. Eight studies (3118 participants) were included in this review. We found no evidence for difference in overall mortality between the groups treated with heparin and placebo (risk ratio (RR) = 0.84, 95% confidence interval (CI) 0.36 to 1.98). Heparins compared with placebo, reduced the occurrence of myocardial infarction in patients with unstable angina and NSTEMI (RR = 0.40, 95% CI 0.25 to 0.63, number needed to benefit (NNTB) = 33). There was a trend towards more major bleeds in the heparin studies compared to control studies (RR = 2.05, 95% CI 0.91 to 4.60). From a limited data set, there appeared to be no difference between patients treated with heparins compared to control in the occurrence of thrombocytopenia (RR = 0.20, 95% CI 0.01 to 4.24). Assessment of overall risk of bias in these studies was limited as most of the studies did not give sufficient detail to allow assessment of potential risk of bias.

Authors' conclusions

Compared with placebo, patients treated with heparins had a similar risk of mortality, revascularization, recurrent angina, and thrombocytopenia. However, those treated with heparins had a decreased risk of myocardial infarction and a higher incidence of minor bleeding. Overall, the evidence assessed in this review was classified as low quality according to the GRADE approach. The results presented in this review must therefore be interpreted with caution.

PLAIN LANGUAGE SUMMARY

Heparins reduce the number of heart attacks but caused more minor bleeding after non-ST elevation acute coronary syndromes compared with placebo

Blood clots in the arteries leading to the heart can cause acute coronary syndromes: unstable angina (a feeling of tightness in the chest) or a type of heart attack (non-ST segment myocardial infarction - NSTEMI). Drugs that prevent clots from forming (such as aspirin) or thin the blood (such as heparin) can relieve the problem. Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are two types of heparin. This review of trials found that UFH and LMWH when given to patients with high-risk unstable angina or NSTEMI in the acute phase of treatment, in addition to standard therapy with aspirin, prevent more heart attacks than placebo but do not reduce mortality, the need for revascularization procedures or recurrent angina. Although there was limited reporting of side-effects, heparins caused more cases of minor bleeding.

SUMMARY OF FINDINGS

Summary of findings 1.   Heparin versus placebo for non-ST elevation acute coronary syndromes

Heparin versus placebo for non-ST elevation acute coronary syndromes

Patient or population: patients with non-ST elevation acute coronary syndromes
Settings: Inpatients
Intervention: Heparin
Comparison: Placebo or untreated control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	ASA	**Heparin + ASA**				
All-cause mortality Follow-up: 5-150 days	Study population		**RR 0.84** (0.36 to 1.98)	2426 (6 studies)	⊕⊕⊖⊖ **low** [1,2,3]	Low due to study limitations and imprecision
	9 per 1000	8 per 1000 (3 to 18)				
	Moderate					
Incidence of myocardial infarction Follow-up: 5-150 days	Study population		**RR 0.4** (0.25 to 0.63)	2426 (6 studies)	⊕⊕⊖⊖ **low** [4]	Low quality because of very serious study limitations
	48 per 1000	19 per 1000 (12 to 30)				
	Moderate					
	58 per 1000	23 per 1000 (15 to 37)				
Recurrent angina Follow-up: 5-150 days	Study population		**RR 0.81** (0.6 to 1.09)	2426 (6 studies)	⊕⊖⊖⊖ **very low** [4,6]	Very low due to study limitations and inconsistency
	166 per 1000	134 per 1000 (99 to 181)				
	Moderate					
	361 per 1000	292 per 1000				

		(217 to 393)				
Incidence of revascularization procedures Follow-up: 5-150 days	**Study population**		**RR 0.93** (0.76 to 1.15)	2520 (6 studies)	⊕⊕⊖⊖ **low** [4]	Low quality because of very serious study limitations
	96 per 1000	90 per 1000 (73 to 111)				
	Moderate					
	135 per 1000	126 per 1000 (103 to 155)				
Major hemorrhage Follow-up: 2-150 days	**Study population**		**RR 2.05** (0.91 to 4.6)	3118 (8 studies)	⊕⊕⊖⊖ **low** [5]	Low quality because of very serious study limitations
	5 per 1000	9 per 1000 (4 to 21)				
	Moderate					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Allocation concealment was uncertain in the majority of the evaluated trials. Lack of blinding of participants and outcome assessors in two trials, blinding of outcome assessors is uncertain in three trials. Final decision: rate down by one level (lack of blinding not considered a serious study limitation for the outcome of all-cause mortality). Two trials stopped early for benefit; stopping early as a source of bias is questionable. Final decision was not to rate down for stopping early for benefit.

[2] Wide confidence intervals and few events. We decided to rate down for imprecision because confidence intervals fails to exclude important benefit or important harm.

[3] Funnel plot could be interpreted as suggesting of publication bias. However, the number of studies is insufficient to meet rigorous criteria for creating a funnel plot. Final decision: publication bias is speculative (not rate down).

[4] Allocation concealment was uncertain in the majority of the evaluated trials. Lack of blinding of participants in four trials, lack of blinding of outcome assessors in two trials, blinding of outcome assessors is uncertain in three trials. Final decision: rate down by two levels.Two trials stopped early for benefit; stopping early as a source of bias is questionable. Final decision was not to rate down for stopping early for benefit.

[5] Allocation concealment was uncertain in the majority of the evaluated trials. Lack of blinding of participants in four trials, lack of blinding of outcome assessors in two trials, blinding of outcome assessors is uncertain in five trials. Final decision: rate down by two levels.Two trials stopped early for benefit; stopping early as a source of bias is questionable. Final decision was not to rate down for stopping early for benefit.

[6] Results were inconsistent across studies as evidenced by $I^2 = 65\%$

Heparin versus placebo for non-ST elevation acute coronary syndromes (Review)

BACKGROUND

Acute coronary syndromes represent a spectrum of disease ranging from unstable angina to non-ST segment myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). The pathophysiology of non-ST segment elevation acute coronary syndromes (NSTEACS), i.e. unstable angina and NSTEMI, involves the rupture or erosion of an atherosclerotic coronary plaque (Falk 1995), activation of the coagulation cascade, and adhesion, activation and platelet aggregation. Inflammation plays a central role in the pathogenesis of atherosclerosis. Macrophage infiltration of plaque is key to this process (Libby 2002). Until recently, a significant proportion of patients admitted with unstable angina progressed to myocardial infarction or died in hospital (Cairns 1989; Cohen 1998).

NSTEMI may be differentiated from unstable angina by the presence of elevated cardiac enzymes indicating actual progression to myocardial necrosis and infarction. Initially, however, the two entities may present identically. Both unstable angina and NSTEMI are differentiated from STEMI in that they are not amenable to either immediate reperfusion therapy with systemic fibrinolytic therapy or immediate percutaneous coronary intervention (PCI). The TIMI III trial assessed the role of fibrinolysis in NSTEACS. This trial evaluated patients with unstable angina or NSTEMI and objective evidence of coronary artery disease. Patients were treated with intravenous heparin and then randomly assigned to placebo or infusion of alteplase. Alteplase administration was not associated with any improvement in primary end points (death or myocardial infarction) at six weeks or one year (Anderson 1995; TIMI IIIB 1994). There was also a trend toward a higher incidence of severe hemorrhagic events in the alteplase group, with intracerebral hemorrhage occurring in four patients versus no controls. Early risk assessment using a risk stratification tool, such as the TIMI risk score is recommended to guide the timing of coronary angiography and possible PCI in patients with NSTEACS (ESC Guidelines NSTEACS 2011).

Given the role of thrombin in the pathogenesis of acute coronary syndromes, heparin has the potential to decrease the occurrence of these undesirable outcomes. Unfractionated heparin (UFH) is a heterogenous mixture of polysaccharide chains whose mechanism of action is mediated through a unique pentasaccharide with a high affinity for antithrombin III. This bond produces a conformational change that increases the ability of antithrombin III to deactivate thrombin, factor Xa and factor IXa. Unfortunately, only one third of the UFH molecules have antithrombin III activity and UFH non-specific binding to protein and cells results in a less predictable dose-response curve (Hirsh 1998). Low molecular weight heparin (LMWH), which is derived from the depolymerization of standard UFH into lower molecular weight fragments, has a number of theoretical advantages including a more predictable dose-response curve, longer half-life and a lower incidence of heparin-induced thrombocytopenia which may be explained by reduced binding to platelets (Weitz 1997). Evidence suggests that LMWH is more efficacious compared to UFH (Eikelboom 2000; Magee 2003), but current guidelines recommend anticoagulation with any form of heparin (LWWH or UFH) for all patients presenting with unstable angina or NSTEMI in addition to antiplatelet therapy (ACCF/AHA Guideline NSTEACS 2013; ESC Guidelines NSTEACS 2011).

Adverse effects of the intervention

Hemorrhage is the chief complication that may result from heparin therapy. By inhibiting blood coagulation, the heparins, generally cause a balancing act between prevention of thrombus formation and inhibition of physiological coagulation. The incidence of bleeding under heparin therapy is hard to define, as it depends on numerous parameters including the indication, dosage, method, and duration of heparin application, the definition of bleeding, patient characteristics and determinants of bleeding such as surgery and co-medication. In clinical trials, up to 30% of patients with acute coronary syndromes or undergoing PCI experience bleeding complications (Manoukian 2007). Heparin-induced thrombocytopenia is a life-threatening disorder that follows exposure to UFH or (less commonly) LMWH. Patients classically present with a low platelet count (<150,000 per cubic millimeter) or a relative decrease of 50% or more from baseline (Warkentin 2003). The incidence of heparin-induced thrombocytopenia is variable and is influenced by the heparin formulation and the clinical context in which heparin is administered.

Why it is important to do this review

Systematic reviews have shown a reduction in the risk of death or myocardial infarction in patients with unstable angina and NSTEMI treated with aspirin plus heparin compared with those treated with aspirin alone (Eikelboom 2000; Oler 1996). Eikelboom et al. assessed the short-term and long-term effects of UFH and LMWH in patients with acute coronary syndromes without ST elevations. The comparisons included UFH and LMWH with placebo or untreated control, and UFH versus LMWH. Overall, short-term UFH or LMWH reduced the incidence of non-fatal myocardial infarction and death by 50%. However, there are some important limitations in these reviews. Firstly, the comprehensiveness of systematic literature searches is far from optimal. For instance, the literature search by Oler et al. was restricted exclusively to MEDLINE (Oler 1996); therefore, it is possible that relevant studies may have been overlooked. Secondly, assessments of risk of bias of studies are not specified in both reviews (Eikelboom 2000; Oler 1996). Assessing the risk of bias of a study can be thought of as assessing the risk that the study results reflect bias in study design or execution rather than the true effect of the intervention or exposure under study. Risk of bias is interchangeable with internal validity and may overlap to a great extent with quality. Given the limitations of previous systematic reviews, we used specific methodology and criteria outlined by The Cochrane Collaboration to present a comprehensive systematic review of heparins (UFH and LMWH) in the acute treatment of NSTEACS.

OBJECTIVES

To update the previously published review that examined the effects of heparin compared with placebo for the treatment of patients with non-ST elevation acute coronary syndromes.

METHODS

Criteria for considering studies for this review

Types of studies

To be considered, clinical studies were required to be randomized controlled trials, including multi-arm trials. Blinding was not a requirement.

Types of participants

Only studies that included adult patients (> 18 years of age) presenting with non-ST elevation acute coronary syndromes requiring treatment within 72 hours of presentation of their last episode of chest pain were considered eligible for inclusion. Non-ST elevation acute coronary syndromes included unstable angina and NSTEMI. Unstable angina had to be characterized as typical chest pain lasting at least 10 minutes within 72 hours of presentation with either historic, electrocardiographic or angiographic evidence of underlying ischemic heart disease. NSTEMI had to be characterized as chest pain with ST segment depression and elevation of relative cardiac enzymes (total creatine kinase (CK) greater than twice the usual upper limit or CK-MB greater than the upper normal limit). Those studies where the patients were inpatients, had stable angina, were volunteers, or presented to non-Emergency Department settings were excluded.

Types of interventions

All patients were required to receive aspirin therapy and be randomized to receive treatment with either parenteral unfractionated heparin (UFH) or low molecular weight heparin (LMWH) compared with placebo or untreated control within 72 hours of presentation. Because platelets play an important role in the development of thrombosis, antiplatelet agents are a mainstay of the treatment of non-ST elevation acute coronary syndromes. Aspirin is recommended by guidelines as acute and long-term treatment for all patients with non-ST elevation acute coronary syndromes unless it is contraindicated (ACCF/AHA Guideline NSTEACS 2013; ESC Guidelines NSTEACS 2011). By the time of the original review, aspirin was the standard of care for patients with unstable angina and NSTEMI.

Intervention

- Parenteral UFH or LMWH.

Comparator

- Placebo or untreated control.

Types of outcome measures

Only studies reporting clinically relevant outcomes were considered. Outcomes over all time periods were considered. Outcomes included the following.

Primary outcomes

- Death (all-cause mortality).
- Myocardial infarction.
- Major hemorrhage (e.g. fall in hemoglobin level of >2 g/dL, requires transfusion, is intracranial, retroperitoneal, or intraocular, or causes death or cessation of the study treatment).

Secondary outcomes

- Recurrent angina (e.g. anginal chest pain that requires nitroglycerin infusion to be restarted).
- Revascularization procedures (e.g. angioplasty with or without stenting, coronary artery bypass grafting).
- Minor hemorrhage (e.g. any clinically important bleed that does not qualify as major; e.g. epistaxis, ecchymosis or hematoma, or macroscopic hematuria).
- Adverse events other than hemorrhage (thrombocytopenia).

Search methods for identification of studies

We updated the previously-run searches from 2002 and searched the following databases up to 15 January 2014:

- Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (2013, Issue 12);
- MEDLINE (OVID, 1946 to January week 1 2014);
- EMBASE Classic + EMBASE (OVID, 1974 to 2014 week 2);
- CINAHL (EBSCO, 1937 to 15 January 2014);
- LILACS (Bireme, 1982 to 15 January 2014).

The search strategies are listed in the Appendix 1. For this update, the randomized controlled trial (RCT) filter for MEDLINE is the Cochrane sensitivity and precision maximizing RCT filter, and for EMBASE, terms as recommended in *the Cochrane Handbook for Systematic Reviews of Interventions* have been applied. (Higgins 2011). The RCT filter for CINAHL is based on SIGN and Cochrane filter terms (Higgins 2011).

Data collection and analysis

Selection of studies

Two review authors (KM and BR) scanned the titles and abstracts of each record retrieved from the searches for the original review. A new review author (CAC) did this for the update. If information in the title and abstract clearly indicated that the trial did not meet the inclusion criteria, we rejected the trial. When a title or abstract could not be rejected with certainty, we obtained the full-text article, and two review authors (KM and BR for original review; CAC and LCL for the update) independently inspected it. We resolved any uncertainties or disagreements on whether papers were eligible for inclusion by consensus in the presence of a third investigator. If we excluded a trial, we recorded both the article citation and the reason for exclusion.

Data extraction and management

For the original review, two review authors (BR, KM) independently extracted data using a standardized form (data extraction sheet based on the Cochrane Consumers and Communication Review Group's data extraction template). Discrepancies were resolved through consensus or in consultation with a third author.

Data extraction included the following items.

- Population: age, gender, time to presentation, inclusion and exclusion criteria
- Type of intervention and control: agent, dose, duration of therapy, weight-based versus fixed dosing, target activated partial thromboplastin time (aPTT), time to adequate aPTT, and control used

- Outcome: timing of primary outcome, assessors, adjudication, definition of: myocardial infarction, unstable angina, mortality
- Side-effect profile: designation of minor and major bleeding
- Design: parallel group versus cross-over; method of randomization, blinding and follow-up

Assessment of risk of bias in included studies

Two review authors (CAC and NDF for the update) independently assessed risk of bias in the included studies using The Cochrane Collaboration 'Risk of bias' tool (Higgins 2011), as described in Chapter 8 of *the Cochrane Handbook for Systematic Reviews of Interventions.* Any disagreements concerning risk of bias were resolved by discussion. We displayed the results by creating a 'Risk of bias' summary (Figure 1) and a 'Risk of bias' graph (Figure 2) using RevMan 5.2 software. For each domain of risk of bias, we described what was reported to have happened in the study in order to provide a rationale for the second part, which involved assigning a judgement of 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk' of bias. For each included study, we assessed the following seven domains of risk of bias.

Figure 1.   'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
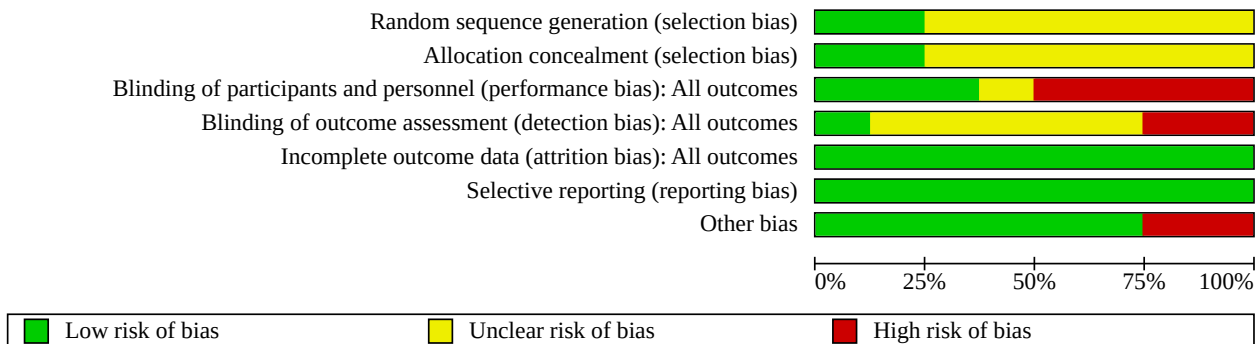
- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selecting reporting (reporting bias)
- Other bias

Measures of treatment effect

All trials were combined using Review Manager, version 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark). For dichotomous variables, individual and pooled statistics were calculated as risk ratios (RR) with 95% confidence intervals (95% CI). DerSimonian–Laird random-effects models (DerSimonian 1987) were used when more than five trials were pooled. When fewer trials or no heterogeneity was identified, a fixed-effect model was employed. If identified, for continuous outcomes, we planned to calculate individual and pooled statistics as mean differences (MD) or standardized mean differences (SMD) and 95% CIs using a random-effects model. The presence of publication bias was examined visually using a funnel plot.

Assesment of heterogeneity

The impact of statistical heterogeneity was quantified using the I^2 statistic. The thresholds of I^2 recommended by *the Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) are:
• 0% to 40%: might not be important;
• 30% to 60%: may represent moderate heterogeneity;
• 50% to 90%: may represent substantial heterogeneity;
• 75% to 100%: considerable heterogeneity.

We used subgroup analyses planned a priori to investigate possible differences between the studies.

Subgroup analysis

Two specific subgroups were planned a priori:

a) Population: unstable angina versus unstable angina and NSTEMI; and
b) Intervention: UFH versus LMWH.

Sensitivity analysis

Possible sources of heterogeneity were assessed by sensitivity analysis that included only trials of good quality. We defined a good-quality study as one which fulfils all of the following criteria: adequate allocation concealment, blinding of outcome assessment and data analysis performed according to the intention-to-treat principle.

Summary of findings

For this update, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for evaluating quality of the evidence of systematic reviews (Higgins 2011) was adopted using the software GRADEprofiler. The quality of the body of evidence was assessed with reference to the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates, and the risk of publication bias. The quality of the body of evidence was classified into four categories: high, moderate, low and very low.

R E S U L T S

Description of studies

Results of the search

The computerized search of EMBASE, MEDLINE and CINAHL of the original review (2002) identified 2193 original publication citations. Independent review of the abstracts and titles of these publications identified 56 potentially relevant studies. Of these potentially relevant articles, eight studies met the inclusion criteria, with a total of 3118 patients being included in this systematic review. One potentially relevant abstract is awaiting assessment as detailed methodology and outcomes have not been possible to obtain (Zwerner 1987).

The 2014 update of the search resulted in 2681 extra citations. One review author (CAC) examined the titles and abstracts and retrieved full-text articles where necessary. This resulted in the addition of nine new references to nine studies (Brown 1964; Cohen 2003; COMPARE 2010; CREATE 2005; Massel 2002; OASIS-6 2006; Oldgren 2008; Peterson 2001; Tanajura 1993). Three additional myocardial infarction studies were considered for inclusion but all study participants had confirmed ST-segment elevation myocardial infarction (STEMI) (Brown 1964; CREATE 2005; OASIS-6 2006).These studies therefore needed to be excluded. The main reasons for

exclusion of the rest of the studies that appeared eligible for this review were (a) not a randomized controlled trial, and (b) heparin not compared versus placebo. The full list of excluded studies and reasons for exclusion are given in the Characteristics of excluded studies.

Included studies

There were no new included studies for this update. Eight studies with a total of 3118 patients treated with either UFH or LMWH were included. In total, 1602 patients (52%) were eligible to receive LMWH and 1508 patients (48%) were eligible to receive UFH. The average age at randomization was 62 years. The majority of trials enrolled male patients (75%) with unstable angina (Doucet 2000; Gurfinkel 1995; Holdright 1994; RISC 1990; Théroux 1988).

Two different LMWHs were used: dalteparin (1498 eligible patients) and nadroparin (104 eligible patients). Of the patients receiving UFH, 19% were switched to warfarin when the UFH was discontinued. Most trials mandated that participants received study medication within 24 hours of the most recent episode of chest pain; however, some patients received it as late as 48 hours in two studies (Cohen 1990; Cohen 1994) and up to 72 hours in two other studies (FRISC 1996; RISC 1990). The duration of treatment varied among the different studies with a range of two to seven days. Aspirin (75 to 325 mg per day) was a standard concomitant intervention in all of the studies. Treatment with other anti-anginal medications (e.g. nitroglycerin, beta-blockers and calcium channel blockers) was at the discretion of the attending physician in most studies. Patients were selected on the basis of narrow inclusion criteria. They had to have a history of unstable angina plus one of the following: a previous history of known coronary artery disease (defined as a prior myocardial infarction, positive exercise stress test or angiographic evidence), ECG changes, or cardiac enzyme elevation. One study (Doucet 2000) stipulated that patients had to present with angina within two weeks to six months following coronary angioplasty.

All studies were RCTs; however, not all were double blind. Three studies (Doucet 2000; Gurfinkel 1995; Holdright 1994) reported on outcomes only over the duration of the hospital admission. In one study (FRISC 1996), only data from the in-patient arm of the study was used although patients were followed up for five to seven months. In all other studies, however, the patients were followed up and the outcomes measured at three months. A variety of outcome measures were reported. Death, myocardial infarction, recurrent angina, revascularization and major bleeds were the most commonly reported outcomes across the studies. One study (Holdright 1994) reported a combined end point of death or myocardial infarction and it was not possible to separate the individual event rates. Death was reported as 'all-cause' and secondary to myocardial infarction in most studies. Myocardial infarction was clearly defined as typical chest pain associated with the appearance of new significant ECG changes (new ST-T changes, loss of R-wave amplitude or development of Q-waves), and the subsequent elevation of serum cardiac enzymes (creatine kinase, plus or minus MB fraction) beyond levels drawn at enrollment. The definition of recurrent angina varied among the studies. Of the six papers which included recurrent angina as a study end point, three required a history of typical chest pain accompanied by ECG changes (Cohen 1990; Cohen 1994; Théroux 1988). The other three studies either did not require associated ST segment changes to diagnose recurrent angina or were unclear how they

defined this end point (Doucet 2000; FRISC 1996; Gurfinkel 1995). The indications for revascularization were not well defined in most studies with 'severe refractory/recurrent ischemia' being the most common criteria. The definition of major bleeding complications was consistent across all studies. Minor bleeds and the incidence of thrombocytopenia were only reported in three and two studies respectively.

The timing of the end points was inconsistent among the trials ranging from 48 hours to three months. In four studies, endpoints were recorded over a five- to eight-day period (Doucet 2000; FRISC 1996; Gurfinkel 1995; Holdright 1994), while in the other four studies, end points were measured at three months (Cohen 1990; Cohen 1994; RISC 1990; Théroux 1988). We have grouped the results for all reported time periods.

Risk of bias in included studies

For this update, two authors (CAC and NDF) independently assessed risk of bias of the trials. For this purpose, instructions given in *the Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) were followed.

Allocation

The sequence generation for participant allocation was adequate in only two studies (FRISC 1996; Théroux 1988). Both studies used blocked randomization to determine the allocation for the two comparison groups. In six studies, the method of sequence generation was unclear or not specified (Cohen 1990; Cohen 1994; Doucet 2000; Gurfinkel 1995; Holdright 1994; RISC 1990). In relation to concealment of the allocation sequence, in two of the studies the pharmacy assigned eligible participants randomly (Doucet 2000; Théroux 1988;). The rest of the studies provided insufficient information about concealment of the allocation sequence (Cohen 1990; Cohen 1994; FRISC 1996; Gurfinkel 1995; Holdright 1994; RISC 1990).

Blinding

Three trials adequately reported blinding of participants (Doucet 2000; FRISC 1996; Théroux 1988), while only one study adequately reported blinding of assessors and personnel (Théroux 1988). Two trials did not blind participants, personnel, or outcome assessors (Cohen 1990; Cohen 1994).Two trials did not blind participants and was unclear about the blinding of assessors (Gurfinkel 1995; Holdright 1994). Blinding of outcome assessors was unclear in five trials (Doucet 2000; FRISC 1996; Gurfinkel 1995; Holdright 1994; RISC 1990).

Incomplete outcome data

The number of missing data was equally distributed between treatment and control group in six trials (Cohen 1990; Cohen 1994; Doucet 2000; FRISC 1996; RISC 1990; Théroux 1988). Two studies reported to have complete data for all included participants (Holdright 1994; Gurfinkel 1995).

Selective reporting

No study protocol was available for the evaluated studies (Cohen 1990; Cohen 1994; Doucet 2000; FRISC 1996; Gurfinkel 1995; Holdright 1994; RISC 1990; Théroux 1988), but all clinically expected outcomes were reported. Publication bias for the incidence of multiple end points (death or myocardial infarction) over all time

periods was examined visually in the form of funnel plot. The funnel plot indicates that there may be publication bias (Figure 3).

However, the number of studies is considered insufficient to meet rigorous criteria for creating a funnel plot (Sterne 2011).

Figure 3. Funnel plot of comparison: 5 Incidence of multiple end points (death or myocardial infarction) over all time periods, outcome: 5.1 Heparin vs placebo or untreated control.
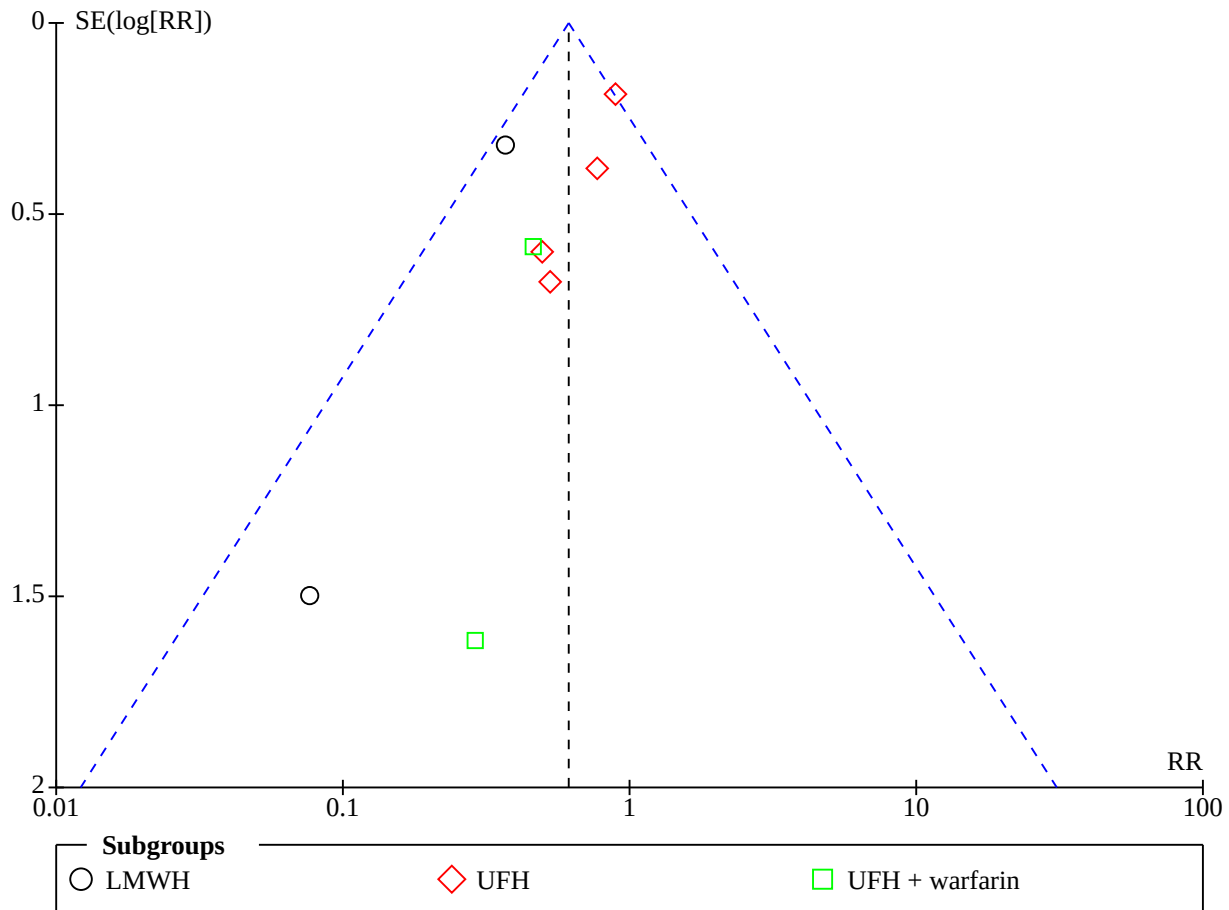
Other potential sources of bias

Two studies (Gurfinkel 1995; Théroux 1988) were stopped early. One of these trials was stopped early due to benefit with nadroparin and more bleeding with heparin (Gurfinkel 1995).The other study was discontinued prematurely on the basis of the policy board (Théroux 1988).

Effects of interventions

See: **Summary of findings 1** Heparin versus placebo for non-ST elevation acute coronary syndromes

As the timing of outcomes varied between studies, the results are tabulated over all time periods.

Primary outcomes

Death

Death was reported as an outcome in six trials involving 2426 patients (Cohen 1990; Cohen 1994; Doucet 2000; FRISC 1996; Gurfinkel 1995; Théroux 1988). The incidence of death in those

treated with placebo was 0.9% (11/1188) compared to 0.7% (9/1238) in those treated with an heparin. Overall, there was a trend towards fewer deaths in the heparin group compared to the placebo group; however, this was not statistically significant (risk ratio (RR) = 0.84, 95% confidence interval (CI) 0.36 to 1.98, P = 0.82, $I^2 = 0\%$) (Analysis 1.1).

Myocardial infarction

Myocardial infarction was reported as an outcome in six trials involving 2426 patients (Cohen 1990; Cohen 1994; Doucet 2000; FRISC 1996; Gurfinkel 1995; Théroux 1988). Heparins were superior to placebo in preventing myocardial infarction (RR = 0.40, 95% CI 0.25 to 0.63, P = 0.63, $I^2 = 0.0\%$). The overall incidence of myocardial infarction was 4.8% (57/1188) in those treated with placebo compared to 1.9% (24/1238) in those treated with heparin. Given the risk difference of -0.03 (95% CI -0.01 to -0.04), 33 (95% CI 25 to 100) patients would need to be treated with either type of heparin to prevent one additional myocardial infarction in patients presenting with acute coronary syndromes (Analysis 2.1).

Major bleeds

All eight trials, involving 3118 patients, reported major bleeds as an outcome (Cohen 1990; Cohen 1994; Doucet 2000; FRISC 1996; Gurfinkel 1995; Holdright 1994; RISC 1990; Théroux 1988). Major bleeding was defined as a fall in hemoglobin of more than 2 g/dL, or bleeding leading to transfusion in seven trials (Cohen 1990; Cohen 1994; Doucet 2000; FRISC 1996; Gurfinkel 1995; Holdright 1994; Théroux 1988). The RISC trial reported no major bleeds (RISC 1990). There was a trend towards more major bleeds in the heparin studies compared to control studies (RR = 2.05, 95% CI 0.91 to 4.60, I^2 = 0.0%). In the two studies that treated patients with warfarin after initial heparin (Cohen 1990; Cohen 1994), there was a trend towards more major bleeds (RR = 7.26, 95% CI 0.38 to 138). No heterogeneity was observed in this outcome (P = 0.93) (Analysis 6.1).

Secondary outcomes

Recurrent angina

Recurrent angina was reported as an outcome in six studies involving 2426 patients (Cohen 1990; Cohen 1994; Doucet 2000; FRISC 1996; Gurfinkel 1995; Théroux 1988). There was evidence of heterogeneity in this data set (P < 0.01) and a random-effects model was used to calculate the pooled statistic. Although heparins as a group showed a trend towards preventing recurrent angina compared to placebo, this result was not statistically significant (RR = 0.81, 95% CI 0.60 to 1.09; I^2 = 65.0%) (Analysis 3.1).

Revascularization procedures

The need for a revascularization procedure was reported as an outcome in six of the eight included studies involving 2520 patients (Cohen 1990; Cohen 1994; Doucet 2000; FRISC 1996; Gurfinkel 1995; Théroux 1988). The pooled results from these studies failed to demonstrate a benefit of heparins compared to aspirin plus placebo in preventing revascularization procedures (RR = 0.93, 95% CI 0.76 to 1.15, I^2 = 41.1%) (Analysis 4.1).

Multiple end points

We were able to calculate the incidence of death or myocardial infarction for all eight included studies (Cohen 1990; Cohen 1994; Doucet 2000; FRISC 1996; Gurfinkel 1995; Holdright 1994; RISC 1990; Théroux 1988). Patients who were treated with heparins were less likely to experience one of these outcomes compared to those treated with placebo (RR = 0.61, 95% CI 0.47 to 0.80, I^2 = 26.5%). No significant heterogeneity was identified in this result (P = 0.22). The incidence of death or myocardial infarction was 4.9% (79/1602) for patients treated with heparins compared to 7.6% (115/1508) for those treated with placebo. Given a risk difference of -0.03 (95% CI -0.01 to -0.05), 33 (95% CI 20 to 100) patients would need to be treated with heparin to prevent one additional death or myocardial infarction (Analysis 5.1).

Minor bleeds

Only three of the eight included studies (n = 1931) reported minor bleeds as an outcome (Cohen 1994; FRISC 1996; Gurfinkel 1995). Data from the analysis indicated heterogeneity (P < 0.03) so a random-effects model was used to pool data. Patients who were treated with heparins experienced significantly more minor bleeds compared to patients treated with placebo (RR = 6.80, 95% CI 1.23

to 37.49, I^2 = 66.9%). In the heparin group, 8.0% (79/989) of patients experienced minor bleeding compared to only 0.5% (5/942) in control group. This represents a risk difference of 0.06 (95% CI 0.02 to 0.11), such that for every 17 (95% CI 9 to 50) patients treated with heparin, one additional case of minor bleeding was observed (Analysis 7.1).

Thrombocytopenia

Only two studies (n = 1717) reported the outcome of thrombocytopenia (FRISC 1996; Gurfinkel 1995). From this limited data set, there appeared to be no difference between patients treated with heparins compared to control in the occurrence of thrombocytopenia (RR = 0.20, 95% CI 0.01 to 4.24, I^2 = 0.0%) (Analysis 8.1).

Sensitivity analysis

Sensitivity analysis based on random-effects versus fixed-effect modeling yielded very similar overall results. With the exception of recurrent angina, the pooled statistic for all other outcomes was essentially unchanged regardless of whether a random-effects or fixed-effect model was chosen. If a fixed-effect instead of a random-effects model had been used for recurrent angina, the point estimate would have essentially remained unchanged; however, the narrowed 95% CIs would result in a statistically significant reduction of recurrent angina with heparins compared to aspirin alone (RR = 0.79, 95% CI 0.67 to 0.93). The trial quality assessment eliminated four papers, approximately 25% of enrolled participants. When this sensitivity analysis (e.g. excluding these studies) was performed, there were no important changes in these pooled results.

Subgroup analysis

Subgroup analysis based on whether patients had unstable angina versus a NSTEMI was not possible in this review, since subgroup data could not be obtained from the studies.

Subgroup comparisons based on whether UFH or LMWH was used were difficult to make due to small study numbers. Of the eight included studies, only two (FRISC 1996; Gurfinkel 1995) compared LMWH versus placebo. It is interesting to note, however, that only the LMWH subgroup showed a statistically significant benefit over the control group in any of the outcomes studies. Higgins and Thompson (Higgins 2003) propose the I^2 statistic which describes the percentage of total variation across studies due to heterogeneity rather than chance. Using their methods, significant and important heterogeneity was identified with respect to the incidence of recurrent angina (P = 0.01 and I^2 = 65%) and revascularization procedures (P = 0.12 and I^2 = 41%). When the data were analyzed according to the treatment received, clinically important subgroups were identified. The pooled analysis from the LMWH subgroup showed statistically significant benefit with respect to the incidence of recurrent angina (P = 0.52; 95% CI 0.36 to 0.74) and revascularization procedures (P = 0.26; 95% CI: 0.09 to 0.78), even though this benefit was lost when all heparins were grouped together.

DISCUSSION

This systematic review examined the best available evidence for the use of heparins in the treatment of non-ST elevation acute coronary syndromes and identified several important outcomes related to

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their use. Overall, heparins as a group failed to demonstrate a statistically significant reduction in mortality, although a beneficial effect as great as a 64% reduction or an increased risk of 98% can not be excluded. Given the low incidence of death in the included studies (~1% to 2%), this systematic review is under-powered to detect small treatment differences. For this outcome, the systematic review had 80% power to detect a relative reduction in risk of 84% (from 0.93% to 0.15%). Approximately 4900 patients in each group would have been required to detect a 50% relative reduction in risk (power = 80%, two-sided alpha = 0.05). Treatment with heparins did, however, reduce the incidence of myocardial infarction such that 33 patients needed to be treated with heparin to prevent one additional myocardial infarction. For most of the other outcomes, the benefit of using heparins was less clear.

Half of all participants randomized to receive heparin in this review were eligible to receive LMWH. When these studies were pooled, LMWH proved to be superior to placebo, not only with reducing the incidence of myocardial infarction, but also with reducing the incidence of recurrent angina and the need for revascularization procedures. Again, although statistically significant, the absolute risk reductions were small (1% to 3%), suggesting caution in the clinical interpretation of these findings.

Overall, little heterogeneity was identified in the pooled results reported in this review. This is not surprising given that non-ST elevation acute coronary syndromes represent a well-defined disease spectrum with fairly clear-cut dichotomous outcomes. Outcomes in which heterogeneity was identified included the incidence of recurrent angina and minor bleeds (I^2 = 65% and 67%, respectively). A moderate degree of heterogeneity was identified (I^2 = 41%) in the incidence of revascularization procedures. This can in part be accounted for by subtle differences in study design: inclusion criteria, dosing regimen, UFH versus LMWH use and timing of outcomes. To a larger extent, however, this heterogeneity may reflect the particular outcomes in question, the definitions of which varied between studies and local practices relating to revascularization procedures.

Overall, heparins appeared to be a safe treatment for non-ST elevation acute coronary syndromes. Although there was a trend towards more major bleeds in the heparin-treated group, this was not statistically significant. Not surprisingly, patients treated with heparins had a higher incidence of minor bleeding. It is difficult to comment on the rate of thrombocytopenia as only two studies commented on this rare, but potentially life-threatening complication of heparinization. This data must be interpreted with caution, however, as side-effects were poorly reported in most studies.

There is a possibility of publication bias in this systematic review. For example, by missing unpublished 'statistically' negative trials we may be over-estimating the effect of heparin treatment. However, a comprehensive search of the published literature for potentially relevant studies was conducted, using a systematic strategy to avoid bias. This was followed by attempts to contact corresponding and first authors. Although no unpublished or negative trials were identified, we recognize that these types of trials may exist. The funnel plot demonstrates asymmetry in the area of small negative trials, so this is a legitimate concern. Given the nature of the research (e.g. expensive, complex, difficult to fund), however, these small negative trials are unlikely, and would

not be expected to influence the results. There is also a possibility of study selection bias. Four trials in which the study group did not receive aspirin or were compared versus a non-aspirin control were excluded (Averkov 1993; Charvat 1989; Serneri 1995; Théroux 1993) because of the well-accepted treatment of acute coronary syndromes with aspirin (Lewis 1983; Oler 1996; Théroux 1988). However, we used two independent review authors, and feel confident that the studies excluded were done so for consistent and appropriate reasons. Our search was comprehensive and has been updated, so it is unlikely that we missed any published trials. Most studies restricted enrollment to patients who had either a documented history of coronary artery disease, ECG changes or cardiac enzyme elevation, which is somewhat different from the patient population traditionally treated with heparins for acute coronary syndrome (Cohen 1990; Cohen 1994; FRISC 1996; Gurfinkel 1995; Théroux 1988).

In recent years, the administration of clopidogrel in addition to aspirin and heparin has been shown to be of benefit as initial medical treatment of patients with unstable angina and NSTEMI. Following the results of the CURE trial (Yusuf 2001), dual antiplatelet treatment with clopidogrel combined with aspirin became the standard of care in patients with NSTEACS (ACCF/AHA Guideline NSTEACS 2013; ESC Guidelines NSTEACS 2011). The evidence evaluated in this review comes from older trials where the use of P2Y12 receptor blockers were not in wide use. Thus, the results of our meta-analysis may not be totally applicable to patients with NSTEACS treated with dual antiplatelet therapy. Recent systematic reviews and meta-analyses of randomized controlled trials have shown that dual therapy with aspirin and clopidogrel is beneficial in patients with acute coronary syndromes with a favorable benefit-risk profile (Bowry 2008; Eshaghian 2007; Zhou 2012). However, as antiplatelet therapy becomes more potent, bleeding risk has become a concern (Zhou 2012).

This systematic review illustrates the potential benefit of using heparins in the early treatment of non-ST elevation acute coronary syndromes. These results are concordant with the most current recommendations made by the American Heart Association (ACCF/AHA Guideline NSTEACS 2013) and similar to two previous reviews (Eikelboom 2000; Oler 1996).The AHA suggests using either LMWH or UFH in patients with unstable angina/NSTEMI in addition to antiplatelet therapy as soon as possible after presentation.

Quality of evidence

A total of eight studies were included in this review with a total of 3118 patients. According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, the quality of the evidence was low for all clinically important outcomes. All the included studies were prospective, randomized controlled trials but only one of the included studies was assessed at low risk of bias (Théroux 1988). For all domains, five studies (62%) were at unclear risk of bias for at least one domain (Doucet 2000; FRISC 1996; Holdright 1994; Gurfinkel 1995; RISC 1990). Three of the included studies were at high risk of bias in two domains (Cohen 1990; Cohen 1994, Gurfinkel 1995) see Summary of findings 1.

Regarding the quality of evidence, we conclude that there is insufficient evidence to draw meaningful conclusions about the benefits and harms of heparins in non-ST elevation acute coronary syndromes. Overall, the methodological quality of trials was far from optimal.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review of randomized controlled trials supports the use of heparins in the early treatment of non-ST elevation acute coronary syndromes. Given in addition to aspirin to patients with a history of typical angina accompanied by either a past medical history of coronary artery disease or ECG/cardiac enzyme changes, heparins reduced the incidence of myocardial infarction, but not mortality. In this review, heparins were given within 24 to 72 hours of the onset of symptoms as a weight-adjusted dose for a five to eight day period, with most studies administering it for two to seven days. The small number of studies makes it impossible to recommend a particular dosing regimen. Indirect comparisons of the pooled results of trials of UFH versus placebo with the pooled results of trials of LMWH versus placebo may be interpreted as suggesting that LMWH is more effective than UFH as a subgroup. However, indirect comparisons are unreliable and potentially misleading because of differences in the kinds of patients randomized, outcome definitions, and treatment regimens.

Implications for research

Despite the strength of the findings of this review, there are several areas in which questions remain unanswered.

- Currently, the optimal time of treatment initiation is unclear. The eight studies examined three different time periods: within 24, 48 and 72 hours. It would be interesting to determine whether the timing of heparin administration (in the emergency department versus on the ward) affects outcomes.
- Given the interventional nature of the investigation and treatment of acute coronary syndromes, the optimal duration of heparin treatment remains controversial. Whether shorter duration treatments might be as effective remains an interesting, yet unresolved, question.
- Patient-centered outcomes such as quality of life have not been studied and are particularly warranted. In addition, considering the cost of these drugs, prospective cost-effectiveness analyses will be desirable.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Cohen 1990

Study characteristics	
Methods	Prospective, randomized, open-label trial
Participants	93 patients (21-75 years old) with unstable angina or NSTEMI. Chest pain occurring within 48 hours of randomization
Interventions	3 treatment groups, Group 1: ASA alone 325 mg (bolus and daily [same dose]) (n = 32) Group 2: Heparin infusion (loading 100 U/kg, then infusion to maintain aPTT at two times control) + warfarin started on day 3 or 4 to maintain INR 2-3 (n = 24) Group 3: ASA (325 mg bolus, then 80 mg daily) + heparin + warfarin (n = 37)

Cohen 1990 *(Continued)*

	Intended duration of heparin infusion was 3-4 days.
Outcomes	Outcomes at 12 weeks.
	Primary outcome: recurrent angina, MI, death
	Secondary outcomes: major/minor bleeding, revascularization
Notes	ASA vs ASA + UFH/warfarin. Used data from group 1 and 3 only.
	Trial therapy was continued for 12 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described. Probably not done.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across groups
Selective reporting (reporting bias)	Low risk	No protocol available, all expected outcomes reported.
Other bias	Low risk	

Cohen 1994

Study characteristics

Methods	Prospective, randomized, open-label, multicenter.
Participants	214 patients (> 21 years old) with unstable angina or NSTEMI. Chest pain occurring within 48 hours of randomization.
Interventions	2 treatment groups,
	Group 1: ASA alone 162.5 mg (bolus and daily [same dose]) (n = 109)
	Group 2: ASA + heparin infusion (loading 100 U/kg, then infusion to maintain aPTT at two times control) + warfarin started on day 3 or 4 to maintain INR 2-3 **(**n = 105**)**
	Intended duration of heparin infusion was 3-4 days

Cohen 1994 (Continued)

Outcomes	Primary outcome (hospital discharge to 12 weeks): recurrent angina, MI, death.
	Secondary outcomes: major bleeding, revascularization
Notes	ASA vs ASA + UFH/warfarin.
	Trial therapy was continued for 12 weeks.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described. Probably not done.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across groups
Selective reporting (reporting bias)	Low risk	No protocol available, all expected outcomes reported.
Other bias	Low risk	

Doucet 2000

Study characteristics

Methods	Prospective, 2 x 2 factorial double-blind, placebo-controlled, randomized trial.
Participants	200 patients hospitalized for unstable angina within 2 weeks to 6 months after angioplasty (excluding those with intracoronary stents).
Interventions	4 treatment groups, ASA 325 mg/d + one of;
	Group 1: intravenous nitroglycerin infusion + placebo UFH (n = 47)
	Group 2: intravenous UFH (heparin bolus followed by infusion) + placebo nitroglycerin (n = 48)
	Group 3: intravenous nitroglycerin + intravenous UFH (n = 48)
	Group 4: placebo nitroglycerin + placebo UFH (n = 48)
	96 patient received UFH + ASA

Doucet 2000 *(Continued)*

	95 patients received ASA
Outcomes	Primary end point: Recurrence of angina at 63+/-30 hours. Safety outcome: serious bleeding (need for transfusion or a fall in hemoglobin of ≥2 g/L).
Notes	Unstable angina was defined as recurrent or increased frequency of chest pain lasting > 5 minutes at rest or with minimal exertion within 24 hours before randomization. In the absence of ischemic ECG, inclusion required independent confirmation of the diagnosis of unstable angina by 2 cardiologists.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process.
Allocation concealment (selection bias)	Low risk	Central allocation (pharmacy-controlled randomization).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel. They used coded medications prepared by the hospital pharmacists. aPTT results know only to the pharmacists (infusion rates of placebo were also modified to maintain blinding).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This study did not address this outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across groups.
Selective reporting (reporting bias)	Low risk	No protocol available, all expected outcomes reported.
Other bias	Low risk	

FRISC 1996

Study characteristics

Methods	Prospective, multicenter double-blind, randomized, placebo-controlled, parallel-group trial
Participants	1506 patients with unstable CAD (unstable angina or non-Q-wave myocardial infarction) admitted to hospital with chest pain within the previous 72 hours.
Interventions	2 treatment groups, ASA 300 mg/d (then 75 mg) + one of; Group 1: dalteparin 120 IU/kg SC twice daily x 6 days, then 7500 IU daily for 35-45 days. Group 2: placebo.
Outcomes	Primary outcome: Difference in the rate of death, new MI during the first 6 days of treatment (acute phase).

FRISC 1996 *(Continued)*

	Secondary outcomes: death and MI after 35-45 days, revascularization procedures, major/minor bleeding, thrombocytopenia and need for IV heparin (nIVH).
Notes	Acute phase data used for death and MI outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization done in blocks
Allocation concealment (selection bias)	Unclear risk	Quote: "Placebo was packaged in matching ampoules and syringes" (identical appearance) but, they don't describe the method of concealment in sufficient detail (it´s unclear if they were sequentially numbered.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel likely.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This study did not address this outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across groups (follow-up was incomplete in 8 patients [5 dalteparin, 3 placebo]).
Selective reporting (reporting bias)	Low risk	No protocol available, all expected outcomes reported.
Other bias	Low risk	

Gurfinkel 1995

Study characteristics

Methods	Prospective, randomized, single-blind trial.
Participants	211 patients (>21 years old) with unstable angina occurring within 24 hours of randomization.
Interventions	3 treatment groups, ASA 200 mg/d + one of; Group 1: ASA + placebo heparin (n = 73) Group 2: ASA + heparin infusion (400 IU/kg body weight per day) preceded by a bolus (5,000 IU) (n = 70) Group 3: ASA + subcutaneous nadroparin calcium (214 [UIC]/kg anti-Xa sc bid) + placebo heparin (n = 68)
Outcomes	In-hospital period or if a primary end point reached (5-7 days) Primary outcome: Recurrent angina, death, MI, urgent revascularization major/minor bleeding, thrombocytopenia.

Gurfinkel 1995 *(Continued)*

Notes	Split control group. Patients had evidence of underlying ischemic heart disease. Analysis was based on intention-to-treat.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described. Probably not done.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This study did not address this outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	No protocol available, all expected outcomes reported.
Other bias	High risk	Trial stopped early (interim analysis revealed benefit with nadroparin and more bleeding with heparin).

Holdright 1994

Study characteristics

Methods	Prospective, randomized, single-blind multicenter trial.
Participants	285 patients (30-75 years old) with unstable angina occurring within 24 hours of randomization.
Interventions	2 treatment groups, ASA 150 mg/d + one of; Group 1: ASA (n = 131) Group 2: ASA + heparin infusion (bolus 5,000 IU, then infusion to maintain aPTT 1.5-2.5 the baseline) (n = 154) Intended duration of heparin infusion was 48 hrs
Outcomes	Outcomes over the duration of the hospital admission. Primary outcome: transient MI, MI, death, revascularization.
Notes	Outcome "MI or death" comes together. Mean duration of hospital stay 7.7 days.

Holdright 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described. Probably not done.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This study did not address this outcome. Quote: "all data were analysed centrally"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	No protocol available, all expected outcomes reported.
Other bias	Low risk	

RISC 1990

Study characteristics

Methods	Prospective, randomized, double-blind, placebo-controlled multicenter trial.
Participants	796 patients (<70 years old) with unstable angina or NSTEMI. Chest pain occurring within previous 4 weeks (randomized to treatment up to 72 hours after admission).
Interventions	4 treatment groups, Group 1: ASA placebo + UFH placebo Group 2: ASA placebo + UFH 5000 U IV 6 hourly x 1 day, then 3750 IV 6 hourly x 4 days Group 3: ASA 75 mg/d + UFH placebo (n = 189) Group 4: ASA 75 mg/d + UFH (same as group 2) (n = 210)
Outcomes	Outcomes at 5 days, 30 days and 90 days. Primary outcome: Death or MI (90 days), revascularization,
Notes	Only used data from groups 3 and 4.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described. Probably not done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Trial labeled as "double-blind" but the study did not address this further
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study did not address this outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across groups. Quote: "After 3 months, 95% of patients remained on treatment with no difference between the aspirin and placebo groups"
Selective reporting (reporting bias)	Low risk	No protocol available, all expected outcomes reported.
Other bias	Low risk	Early conclusion of the study recommended by the safety committee, the follow-up was planned for 1 year (it was reduced to 3 months), probably not a risk of bias for this

Théroux 1988

Study characteristics

Methods	Prospective, randomized, double-blind study
Participants	479 patients with unstable angina (admitted or while hospitalized), within 24 hours preceding the time of randomization
Interventions	4 treatment groups (6 days of therapy), Group 1: ASA 650 mg, then 325 mg bid + UFH placebo (n = 121) Group 2: UFH 5000 U, then 1000 U/hour + placebo ASA Group 3: ASA 650 mg, then 325 mg bid + UFH 5000 U IV, then 1000 U/hour (n = 122) Group 4: placebo + placebo UFH
Outcomes	Primary outcome (6 days and 3 months): refractory angina, MI, death, serious (major) bleeding
Notes	Study was discontinued prematurely on the basis of first interim data analysis. Use only data from Groups 1 and 3

Risk of bias

Bias	Authors' judgement	Support for judgement

Théroux 1988 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomization done in blocks
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomization (central)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding probably ensured. Quote: "trial medication prepackaged and coded by the pharmacists on a randomized, double-blind basis"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Some key study personnel probably not blinded, but, outcome measurement are not likely to be influenced by the lack of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	No protocol available, all expected outcomes reported.
Other bias	High risk	The study was discontinued prematurely on the basis of the policy board recommendation after the first interim data analysis

aPTT - activated partial thromboplastin time
ASA - aspirin
CAD - coronary artery disease
INR - international normalized ratio
IV - intravenous
MI - myocardial infarction
NSTEMI - non-ST segment myocardial infarction
SC - subcutaneous
UFH - unfractionated heparin

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

Study	Reason for exclusion
Averkov 1993	Not all patients treated with ASA
Bodo 1995	Not a randomized controlled trial
Borja 2000a	Not a randomized controlled trial
Borja 2000b	Not a randomized controlled trial
Borja 2000c	Not a randomized controlled trial
Brown 1964	Patients had ST-segment elevation MI
Charvat 1989	Not all patients treated with ASA
Cohen 1993	Unclear from results to which study group participants had been randomized. Attempts to communicate with authors unsuccessful.

Study	Reason for exclusion
Cohen 2003	Heparin not compared versus placebo
Collins 1996	Not a randomized controlled trial
COMPARE 2010	Patients not compared to placebo
Correia 1995	Patients not compared to placebo
CREATE 2005	Patients had ST-segment elevation MI
FAMI 2000	No control group in the acute phase of the study
Ferguson 1999	Not a randomized controlled trial
FRISC II 1999	Patients randomized greater than 72 hrs after most recent chest pain
Fujita 1988	Not the research question
GISSI-2 1990	Patients had ST-segment elevation MI
Gorski 1993	Not a randomized controlled trial
Goy 1999	Not a randomized controlled trial
Gulba 1992	Not a randomized controlled trial
Hasselblad 1998	Not a randomized controlled trial
Huber 1989	Not all patients treated with ASA
Hurtado 1984	Patients had ST-segment elevation MI
Jaffrani 1993	Not a randomized controlled trial
Kaul 2000	Not a randomized controlled trial
Kontny 2001	Not a randomized controlled trial
Massel 2002	Not a randomized controlled trial
Mattioli 1999	Heparin not compared versus placebo
Milonig-Ganner 1989	Not a randomized controlled trial
Moise 1994	Not a randomized controlled trial
Montgomery 1995	Not a randomized controlled trial
Nardelli 1991	Not a randomized controlled trial
OASIS-6 2006	Patients had ST-segment elevation MI
Ocampo 1998	Heparin not compared versus placebo
Oldgren 2008	Not a randomized controlled trial

Study	Reason for exclusion
Oler 1996	Not a randomized controlled trial
Peterson 2001	Not a randomized controlled trial
PURSUIT 2001	Not the study question
Raschke 1993	Not the study question
Rubio-Terres 2001	Not a randomized controlled trial
Sayen 1982	Not a randomized controlled trial
Serneri 1988	Outpatient setting
Serneri 1990	Not all patients treated with ASA; only inpatients were admitted into the study
Serneri 1995	Not all patients treated with ASA
Spodick 1989	Not a randomized controlled trial
Tanajura 1993	Outpatient setting, no patients with acute coronary syndromes
TETAMI 2000	Not a randomized controlled trial
Théroux 1993	Not all patients treated with ASA
Thieuleux 1985	Not a randomized controlled trial
Umans 1997	Not a randomized controlled trial
Violaris 1991	Not a randomized controlled trial
Wallentin 1997	Not a randomized controlled trial
Wallis 1991	Not a randomized controlled trial

ASA - aspirin
MI - myocardial infarction

DATA AND ANALYSES

Comparison 1. Incidence of death over all time periods

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Heparin vs placebo or untreated control	6	2426	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.36, 1.98]
1.1.1 LMWH	2	1602	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.33, 2.45]
1.1.2 UFH	3	541	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.3 UFH + warfarin	2	283	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.15, 7.24]

Analysis 1.1.   Comparison 1: Incidence of death over all time periods, Outcome 1: Heparin vs placebo or untreated control

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.1.1 LMWH							
FRISC 1996	7	741	8	757	69.5%	0.89 [0.33 , 2.45]	
Gurfinkel 1995	0	68	0	36		Not estimable	
Subtotal (95% CI)		**809**		**793**	**69.5%**	**0.89 [0.33 , 2.45]**	
Total events:	7		8				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.22 (P = 0.83)							
1.1.2 UFH							
Doucet 2000	0	95	0	96		Not estimable	
Gurfinkel 1995	0	70	0	37		Not estimable	
Théroux 1988	0	122	1	121	13.2%	0.33 [0.01 , 8.04]	
Subtotal (95% CI)		**287**		**254**	**13.2%**	**0.33 [0.01 , 8.04]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.50)							
1.1.3 UFH + warfarin							
Cohen 1990	0	37	0	32		Not estimable	
Cohen 1994	2	105	2	109	17.2%	1.04 [0.15 , 7.24]	
Subtotal (95% CI)		**142**		**141**	**17.2%**	**1.04 [0.15 , 7.24]**	
Total events:	2		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.04 (P = 0.97)							
Total (95% CI)		**1238**		**1188**	**100.0%**	**0.84 [0.36 , 1.98]**	
Total events:	9		11				
Heterogeneity: Chi² = 0.39, df = 2 (P = 0.82); I² = 0%							
Test for overall effect: Z = 0.39 (P = 0.70)							
Test for subgroup differences: Chi² = 0.39, df = 2 (P = 0.82), I² = 0%							

Favours treatment   0.01 0.1 1 10 100   Favours control

Comparison 2.   Incidence of MI over all time periods

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Heparin vs placebo or untreated control	6	2426	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.25, 0.63]
2.1.1 LMWH	2	1602	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.14, 0.55]
2.1.2 UFH	3	541	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.23, 1.34]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1.3 UFH + warfarin	2	283	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.25, 1.62]

Analysis 2.1. Comparison 2: Incidence of MI over all time periods, Outcome 1: Heparin vs placebo or untreated control

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.1.1 LMWH							
FRISC 1996	10	741	33	757	54.5%	0.31 [0.15 , 0.62]	
Gurfinkel 1995	0	68	3	36	7.6%	0.08 [0.00 , 1.44]	
Subtotal (95% CI)		**809**		**793**	**62.1%**	**0.28 [0.14 , 0.55]**	
Total events:	10		36				
Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%							
Test for overall effect: Z = 3.70 (P = 0.0002)							
2.1.2 UFH							
Doucet 2000	0	95	0	96		Not estimable	
Gurfinkel 1995	4	70	4	37	8.7%	0.53 [0.14 , 1.99]	
Théroux 1988	4	122	7	121	11.7%	0.57 [0.17 , 1.89]	
Subtotal (95% CI)		**287**		**254**	**20.5%**	**0.55 [0.23 , 1.34]**	
Total events:	8		11				
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%							
Test for overall effect: Z = 1.31 (P = 0.19)							
2.1.3 UFH + warfarin							
Cohen 1990	0	37	1	32	2.7%	0.29 [0.01 , 6.87]	
Cohen 1994	6	105	9	109	14.7%	0.69 [0.26 , 1.88]	
Subtotal (95% CI)		**142**		**141**	**17.4%**	**0.63 [0.25 , 1.62]**	
Total events:	6		10				
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.61); I² = 0%							
Test for overall effect: Z = 0.96 (P = 0.34)							
Total (95% CI)		**1238**		**1188**	**100.0%**	**0.40 [0.25 , 0.63]**	
Total events:	24		57				
Heterogeneity: Chi² = 3.44, df = 5 (P = 0.63); I² = 0%							
Test for overall effect: Z = 3.93 (P < 0.0001)							
Test for subgroup differences: Chi² = 2.43, df = 2 (P = 0.30), I² = 17.6%							

0.01 0.1 1 10 100
Favours treatment   Favours control

Comparison 3. Incidence of recurrent angina over all time periods

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 Heparin vs placebo or untreated control	6	2426	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.60, 1.09]
3.1.1 LMWH	2	1602	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.36, 0.74]
3.1.2 UFH	3	541	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.78, 1.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.3 UFH + warfarin	2	283	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.45, 1.87]

Analysis 3.1. Comparison 3: Incidence of recurrent angina over all time periods, Outcome 1: Heparin vs placebo or untreated control

	Treatment		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.1.1 LMWH							
FRISC 1996	28	741	58	757	15.6%	0.49 [0.32, 0.77]	
Gurfinkel 1995	14	68	13	36	11.4%	0.57 [0.30, 1.08]	
Subtotal (95% CI)		**809**		**793**	**27.0%**	**0.52 [0.36, 0.74]**	
Total events:	42		71				
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%							
Test for overall effect: Z = 3.58 (P = 0.0003)							
3.1.2 UFH							
Doucet 2000	56	95	56	96	20.5%	1.01 [0.80, 1.28]	
Gurfinkel 1995	31	70	14	37	14.5%	1.17 [0.72, 1.91]	
Théroux 1988	13	122	20	121	11.1%	0.64 [0.34, 1.24]	
Subtotal (95% CI)		**287**		**254**	**46.1%**	**0.99 [0.78, 1.24]**	
Total events:	100		90				
Heterogeneity: Tau² = 0.01; Chi² = 2.22, df = 2 (P = 0.33); I² = 10%							
Test for overall effect: Z = 0.11 (P = 0.91)							
3.1.3 UFH + warfarin							
Cohen 1990	23	37	16	32	15.9%	1.24 [0.81, 1.91]	
Cohen 1994	12	105	20	109	10.9%	0.62 [0.32, 1.21]	
Subtotal (95% CI)		**142**		**141**	**26.8%**	**0.92 [0.45, 1.87]**	
Total events:	35		36				
Heterogeneity: Tau² = 0.19; Chi² = 3.28, df = 1 (P = 0.07); I² = 70%							
Test for overall effect: Z = 0.23 (P = 0.82)							
Total (95% CI)		**1238**		**1188**	**100.0%**	**0.81 [0.60, 1.09]**	
Total events:	177		197				
Heterogeneity: Tau² = 0.10; Chi² = 17.16, df = 6 (P = 0.009); I² = 65%							
Test for overall effect: Z = 1.41 (P = 0.16)							
Test for subgroup differences: Chi² = 8.84, df = 2 (P = 0.01), I² = 77.4%							

0.01 0.1 1 10 100
Favours treatment   Favours control

Comparison 4. Incidence of revascularization procedures over all time periods

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Heparin vs placebo or untreated control	6	2520	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.76, 1.15]
4.1.1 LMWH	2	1602	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.09, 0.78]
4.1.2 UFH	3	635	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.76, 1.25]

![Cochrane Library logo] Trusted evidence. Informed decisions. Better health.

Cochrane Database of Systematic Reviews

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.1.3 UFH + warfarin	2	283	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.75, 1.74]

Analysis 4.1. Comparison 4: Incidence of revascularization procedures over all time periods, Outcome 1: Heparin vs placebo or untreated control

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.1.1 LMWH							
FRISC 1996	3	741	9	757	7.3%	0.34 [0.09 , 1.25]	
Gurfinkel 1995	1	68	4	36	4.3%	0.13 [0.02 , 1.14]	
Subtotal (95% CI)		809		793	11.5%	**0.26 [0.09 , 0.78]**	
Total events:	4		13				
Heterogeneity: Chi² = 0.54, df = 1 (P = 0.46); I² = 0%							
Test for overall effect: Z = 2.40 (P = 0.02)							
4.1.2 UFH							
Gurfinkel 1995	7	70	5	37	5.3%	0.74 [0.25 , 2.17]	
Holdright 1994	19	154	15	131	13.2%	1.08 [0.57 , 2.03]	
Théroux 1988	56	122	57	121	46.6%	0.97 [0.74 , 1.28]	
Subtotal (95% CI)		346		289	65.2%	**0.98 [0.76 , 1.25]**	
Total events:	82		77				
Heterogeneity: Chi² = 0.35, df = 2 (P = 0.84); I² = 0%							
Test for overall effect: Z = 0.19 (P = 0.85)							
4.1.3 UFH + warfarin							
Cohen 1990	22	37	12	32	10.5%	1.59 [0.94 , 2.67]	
Cohen 1994	12	105	16	109	12.8%	0.78 [0.39 , 1.57]	
Subtotal (95% CI)		142		141	23.3%	**1.14 [0.75 , 1.74]**	
Total events:	34		28				
Heterogeneity: Chi² = 2.68, df = 1 (P = 0.10); I² = 63%							
Test for overall effect: Z = 0.62 (P = 0.54)							
Total (95% CI)		1297		1223	100.0%	**0.93 [0.76 , 1.15]**	
Total events:	120		118				
Heterogeneity: Chi² = 10.18, df = 6 (P = 0.12); I² = 41%							
Test for overall effect: Z = 0.65 (P = 0.51)							
Test for subgroup differences: Chi² = 6.07, df = 2 (P = 0.05), I² = 67.0%							

0.01 0.1 1 10 100
Favours treatment   Favours control

Comparison 5. Incidence of multiple end points (death or myocardial infarction) over all time periods

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 Heparin vs placebo or untreated control	8	3110	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.47, 0.80]
5.1.1 LMWH	2	1602	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.18, 0.61]
5.1.2 UFH	5	1225	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.58, 1.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1.3 UFH + warfarin	2	283	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.15, 1.28]

Analysis 5.1. Comparison 5: Incidence of multiple end points (death or myocardial infarction) over all time periods, Outcome 1: Heparin vs placebo or untreated control

| Study or Subgroup | Treatment | | Control | | Weight | Risk Ratio | Risk Ratio |
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
5.1.1 LMWH							
FRISC 1996	13	741	36	757	29.2%	0.37 [0.20 , 0.69]	
Gurfinkel 1995	0	68	3	36	3.7%	0.08 [0.00 , 1.44]	
Subtotal (95% CI)		**809**		**793**	**33.0%**	**0.34 [0.18 , 0.61]**	
Total events:	13		39				
Heterogeneity: Chi² = 1.06, df = 1 (P = 0.30); I² = 6%							
Test for overall effect: Z = 3.55 (P = 0.0004)							
5.1.2 UFH							
Doucet 2000	0	95	0	96		Not estimable	
Gurfinkel 1995	4	70	4	37	4.3%	0.53 [0.14 , 1.99]	
Holdright 1994	42	154	40	131	35.5%	0.89 [0.62 , 1.29]	
RISC 1990	12	210	14	189	12.1%	0.77 [0.37 , 1.63]	
Théroux 1988	4	122	8	121	6.6%	0.50 [0.15 , 1.60]	
Subtotal (95% CI)		**651**		**574**	**58.5%**	**0.80 [0.58 , 1.08]**	
Total events:	62		66				
Heterogeneity: Chi² = 1.38, df = 3 (P = 0.71); I² = 0%							
Test for overall effect: Z = 1.45 (P = 0.15)							
5.1.3 UFH + warfarin							
Cohen 1990	0	37	1	32	1.3%	0.29 [0.01 , 6.87]	
Cohen 1994	4	105	9	109	7.2%	0.46 [0.15 , 1.45]	
Subtotal (95% CI)		**142**		**141**	**8.6%**	**0.43 [0.15 , 1.28]**	
Total events:	4		10				
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%							
Test for overall effect: Z = 1.52 (P = 0.13)							
Total (95% CI)		**1602**		**1508**	**100.0%**	**0.61 [0.47 , 0.80]**	
Total events:	79		115				
Heterogeneity: Chi² = 9.52, df = 7 (P = 0.22); I² = 26%							
Test for overall effect: Z = 3.62 (P = 0.0003)							
Test for subgroup differences: Chi² = 6.81, df = 2 (P = 0.03), I² = 70.6%							

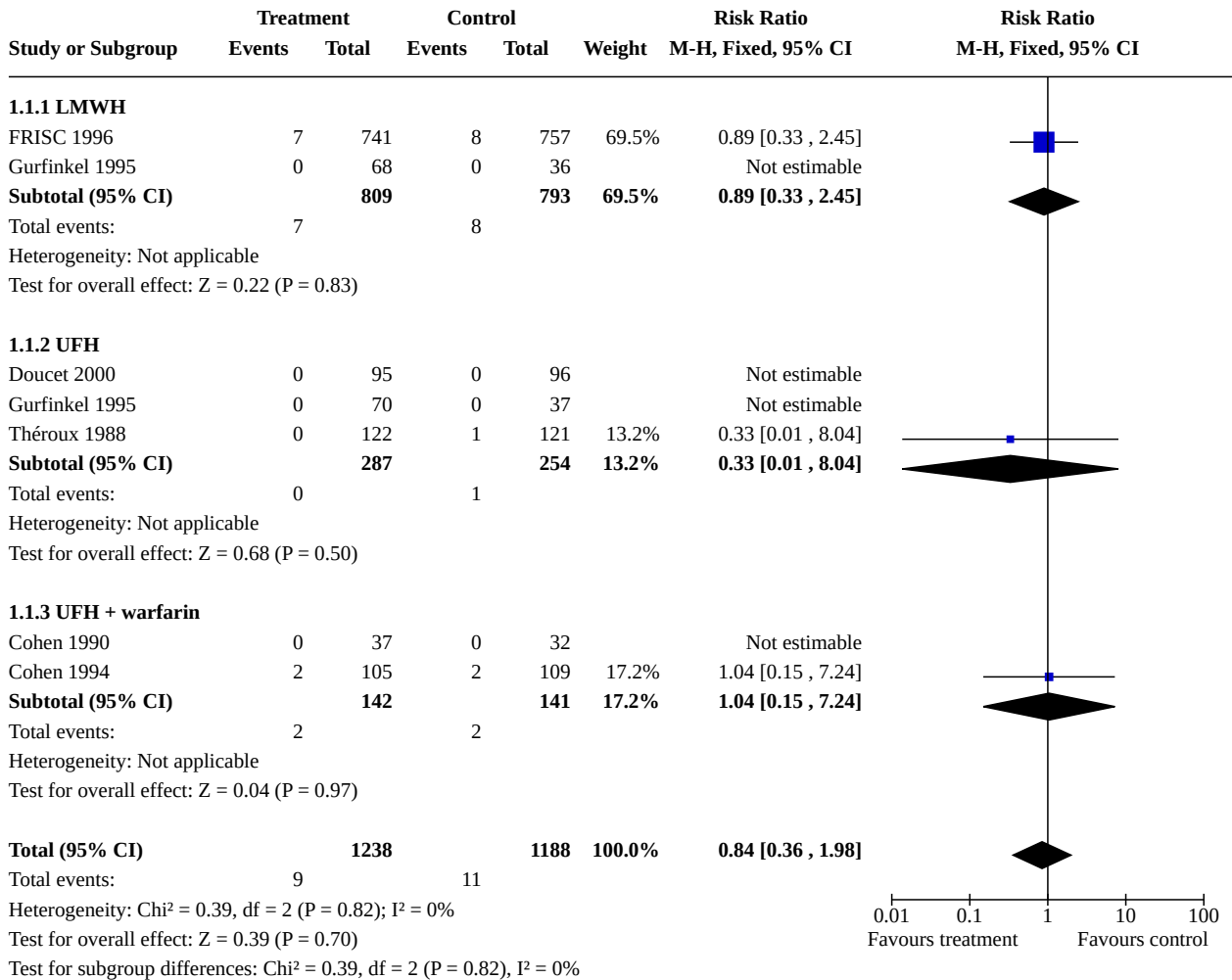0.01 0.1 1 10 100
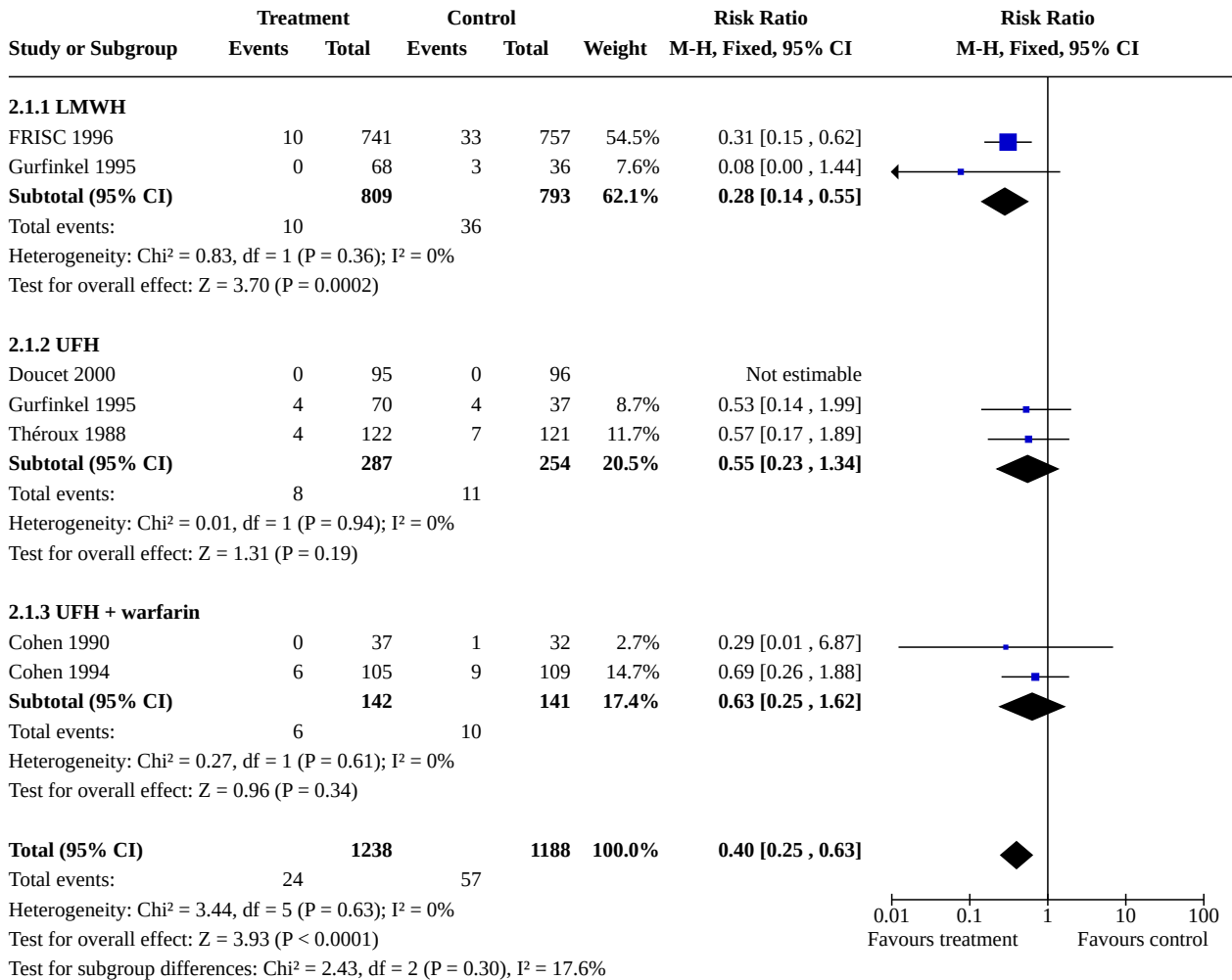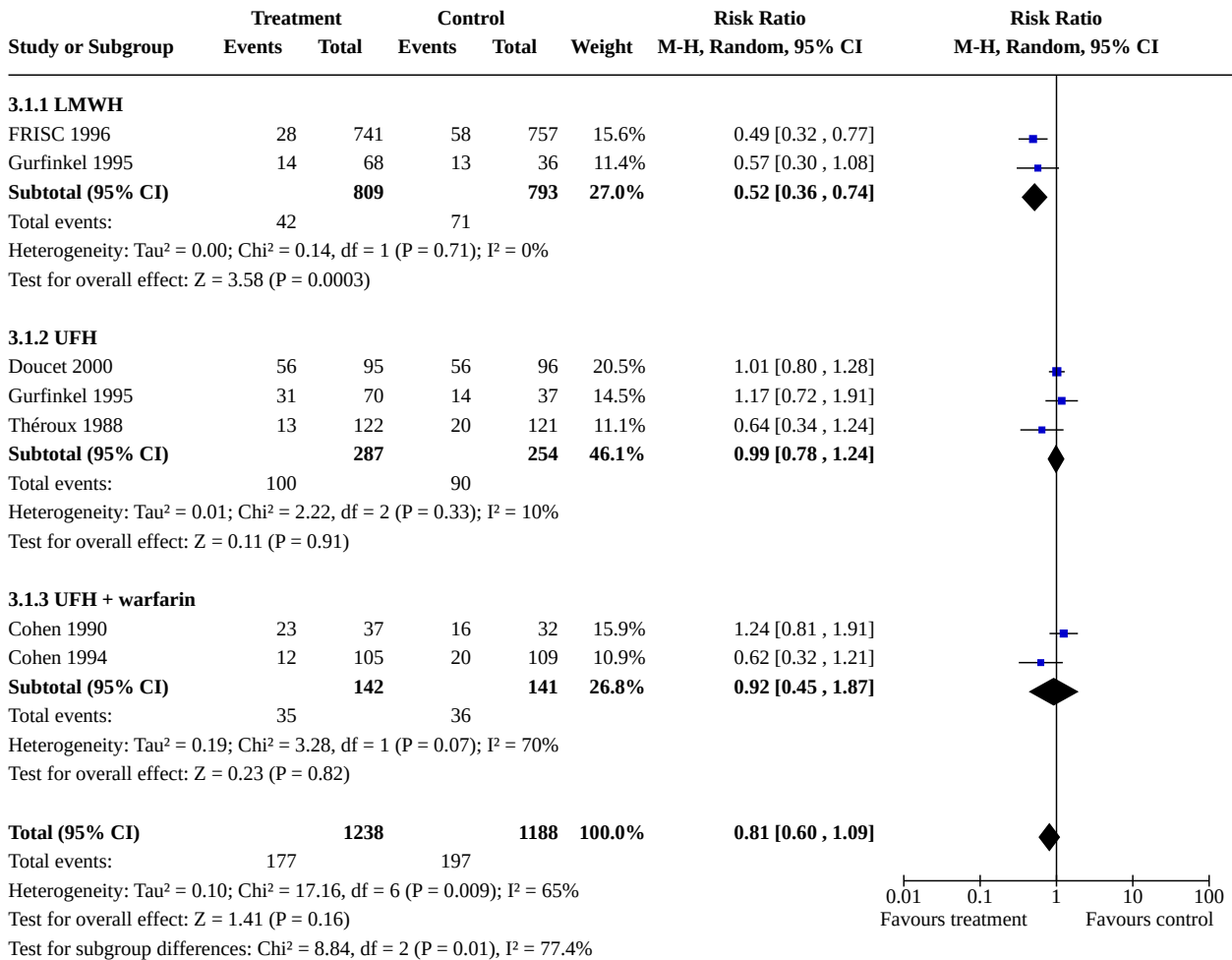Favours treatment   Favours control

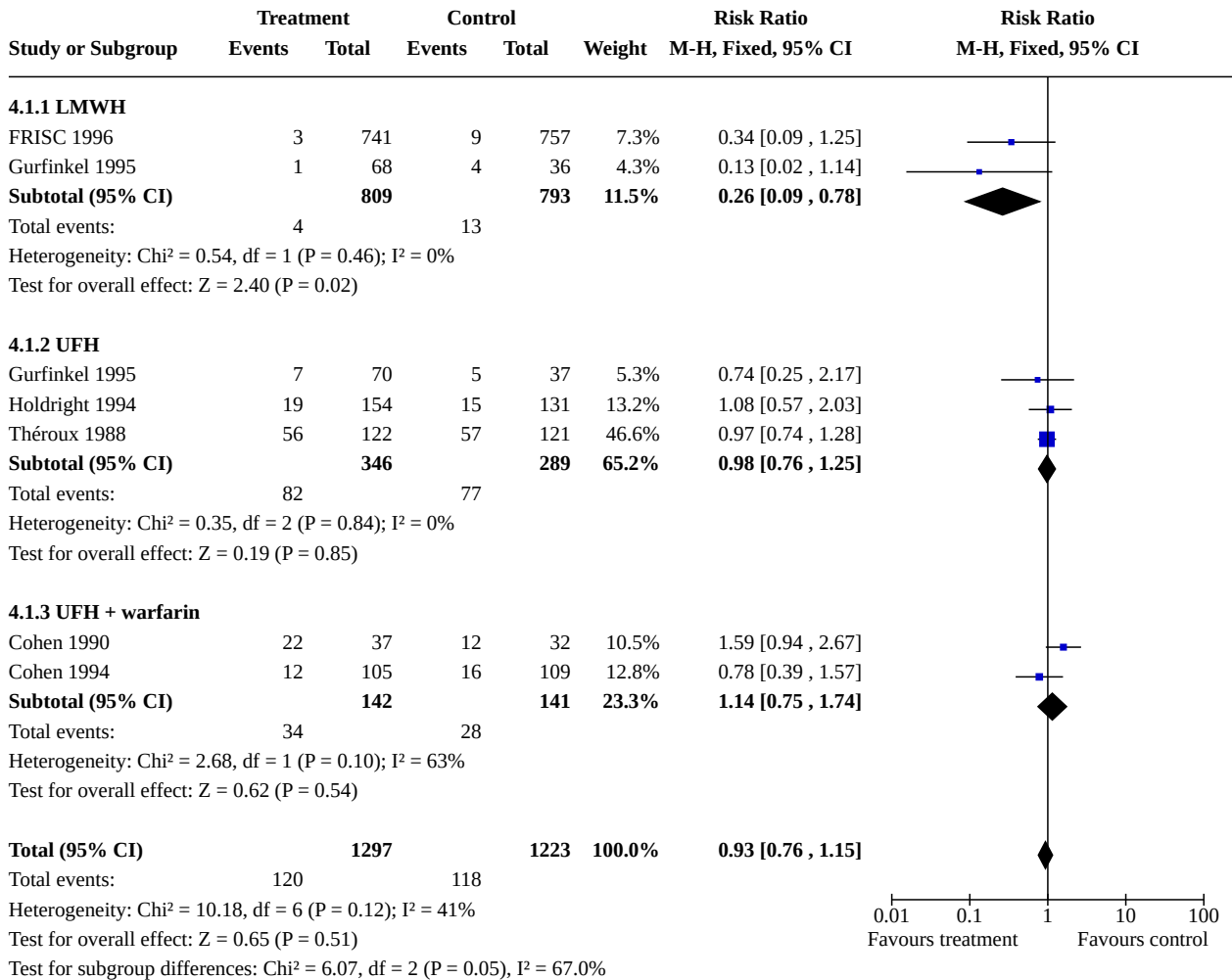### Comparison 6. Incidence of major bleeds over all time periods

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Heparin vs placebo or untreated control	8	3118	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.91, 4.60]
6.1.1 LMWH	2	1610	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.43, 5.39]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1.2 UFH	5	1225	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [0.59, 6.26]
6.1.3 UFH + warfarin	2	283	Risk Ratio (M-H, Fixed, 95% CI)	7.26 [0.38, 138.95]

Analysis 6.1. Comparison 6: Incidence of major bleeds over all time periods, Outcome 1: Heparin vs placebo or untreated control

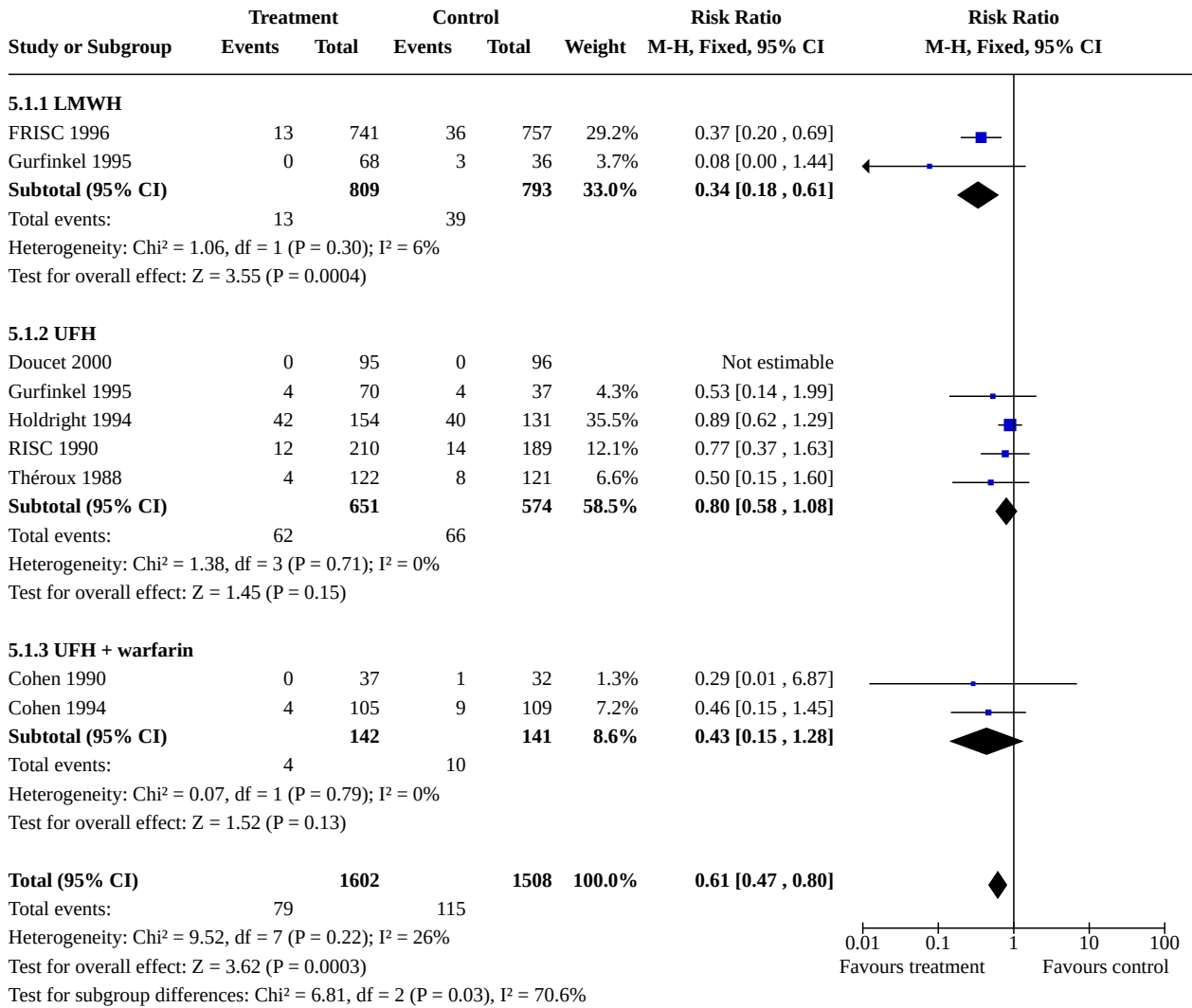| Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
6.1.1 LMWH							
FRISC 1996	6	746	4	760	45.6%	1.53 [0.43 , 5.39]	
Gurfinkel 1995	0	68	0	36		Not estimable	
Subtotal (95% CI)		**814**		**796**	**45.6%**	**1.53 [0.43 , 5.39]**	
Total events:	6		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.66 (P = 0.51)							
6.1.2 UFH							
Doucet 2000	1	95	0	96	5.7%	3.03 [0.13 , 73.49]	
Gurfinkel 1995	2	70	0	37	7.5%	2.68 [0.13 , 54.33]	
Holdright 1994	1	154	1	131	12.4%	0.85 [0.05 , 13.47]	
RISC 1990	0	210	0	189		Not estimable	
Théroux 1988	4	122	2	121	23.1%	1.98 [0.37 , 10.63]	
Subtotal (95% CI)		**651**		**574**	**48.8%**	**1.92 [0.59 , 6.26]**	
Total events:	8		3				
Heterogeneity: Chi² = 0.46, df = 3 (P = 0.93); I² = 0%							
Test for overall effect: Z = 1.09 (P = 0.28)							
6.1.3 UFH + warfarin							
Cohen 1990	0	37	0	32		Not estimable	
Cohen 1994	3	105	0	109	5.6%	7.26 [0.38 , 138.95]	
Subtotal (95% CI)		**142**		**141**	**5.6%**	**7.26 [0.38 , 138.95]**	
Total events:	3		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.32 (P = 0.19)							
Total (95% CI)		**1607**		**1511**	**100.0%**	**2.05 [0.91 , 4.60]**	
Total events:	17		7				
Heterogeneity: Chi² = 1.39, df = 5 (P = 0.93); I² = 0%							
Test for overall effect: Z = 1.73 (P = 0.08)							
Test for subgroup differences: Chi² = 0.91, df = 2 (P = 0.64), I² = 0%							

0.01 0.1 1 10 100
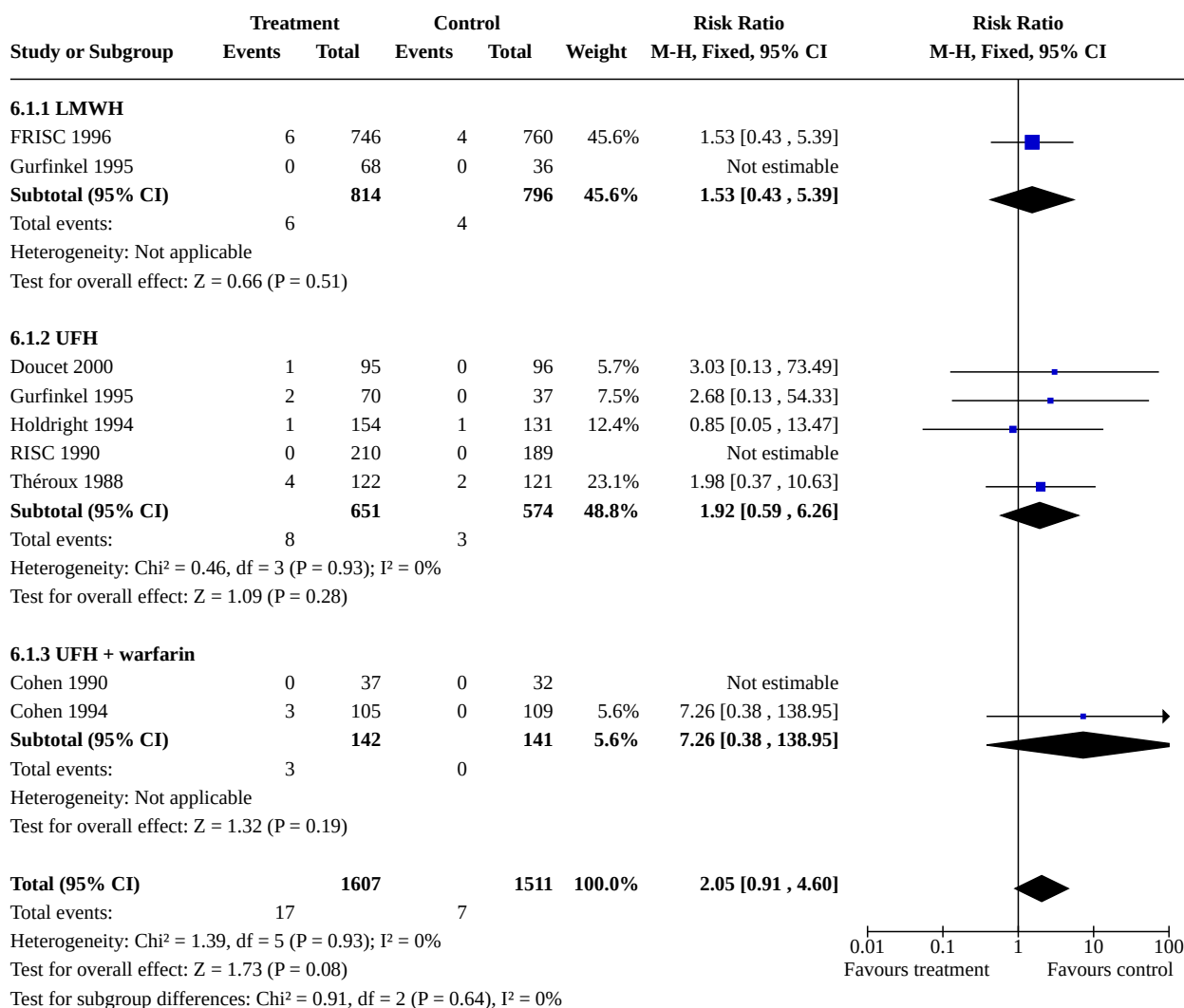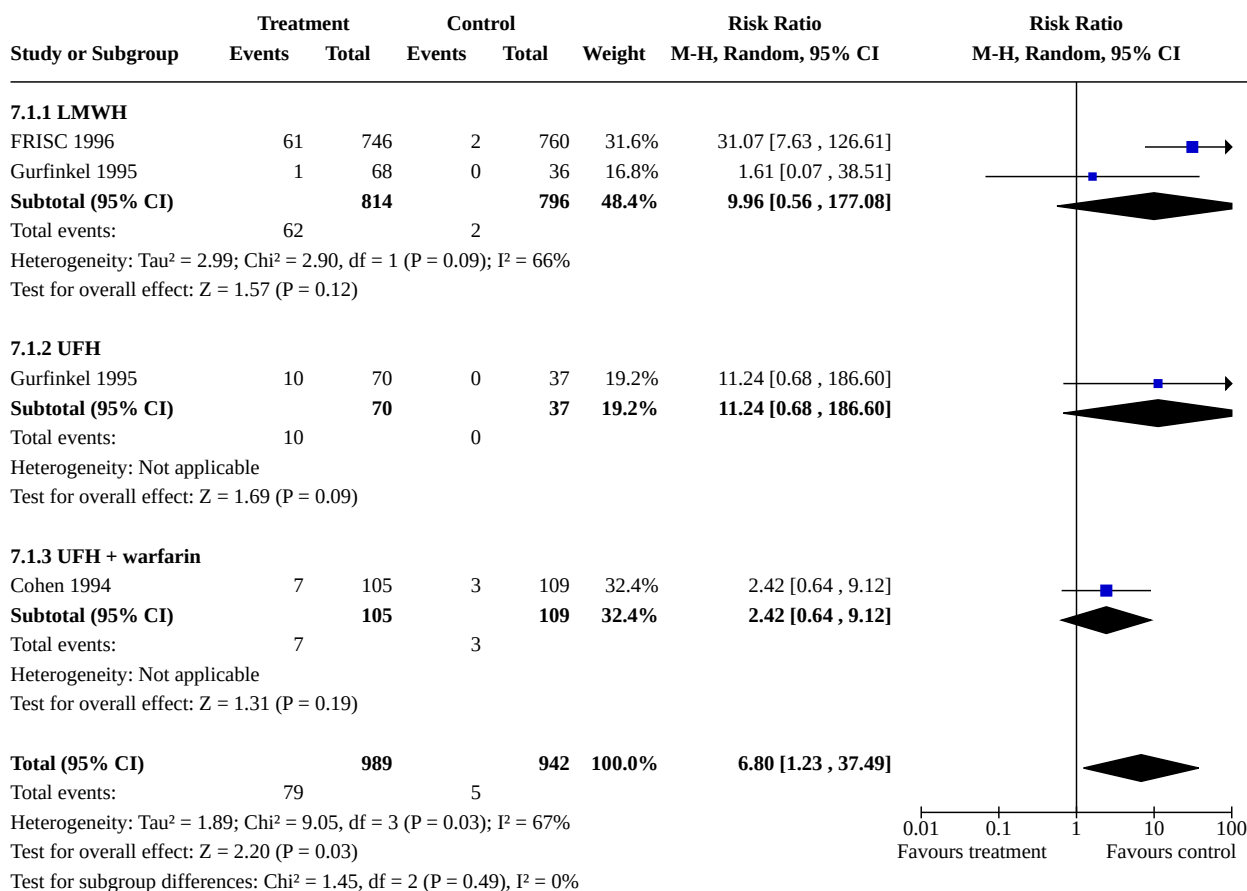Favours treatment — Favours control

Comparison 7. Incidence of minor bleeds over all time periods

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Heparin vs placebo or untreated control	3	1931	Risk Ratio (M-H, Random, 95% CI)	6.80 [1.23, 37.49]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.1.1 LMWH	2	1610	Risk Ratio (M-H, Random, 95% CI)	9.96 [0.56, 177.08]
7.1.2 UFH	1	107	Risk Ratio (M-H, Random, 95% CI)	11.24 [0.68, 186.60]
7.1.3 UFH + warfarin	1	214	Risk Ratio (M-H, Random, 95% CI)	2.42 [0.64, 9.12]

Analysis 7.1. Comparison 7: Incidence of minor bleeds over all time periods, Outcome 1: Heparin vs placebo or untreated control
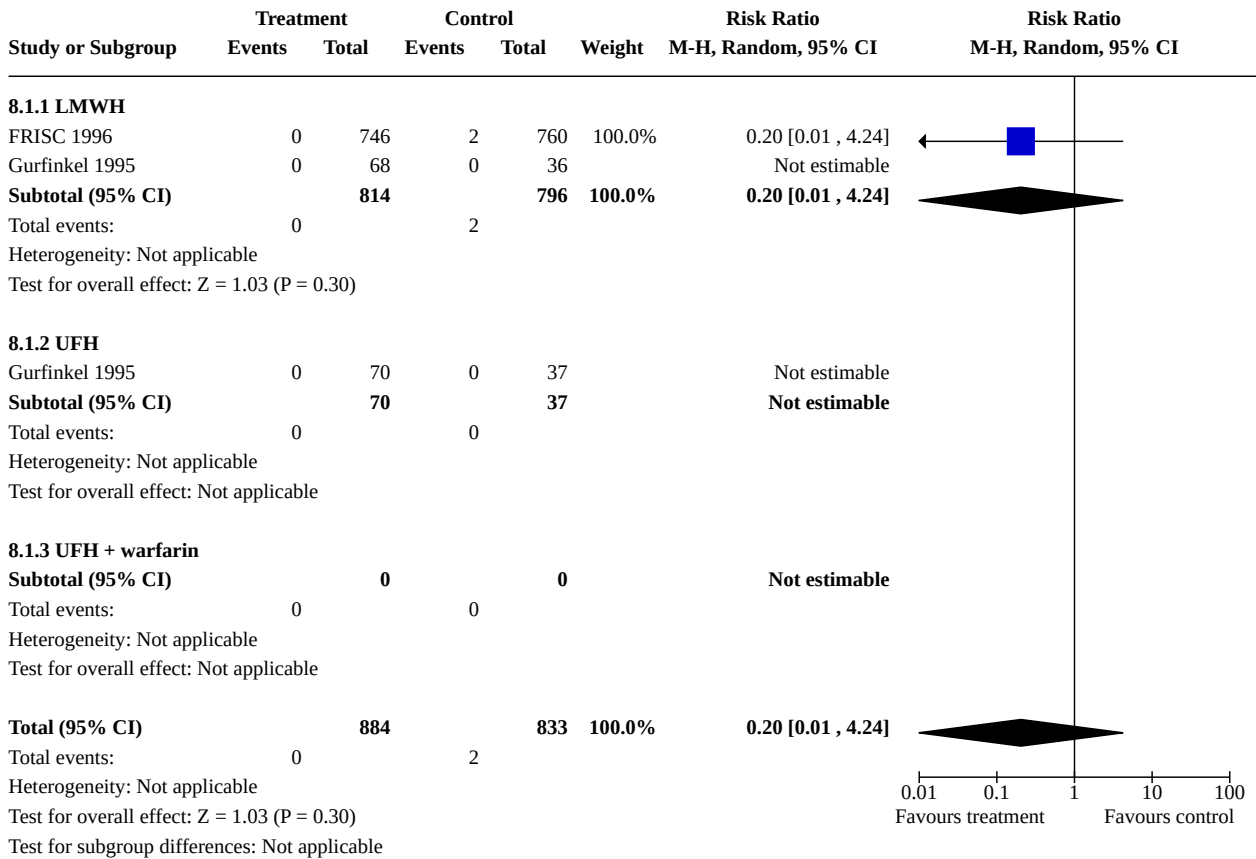
Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.1.1 LMWH							
FRISC 1996	61	746	2	760	31.6%	31.07 [7.63 , 126.61]	
Gurfinkel 1995	1	68	0	36	16.8%	1.61 [0.07 , 38.51]	
Subtotal (95% CI)		814		796	48.4%	**9.96 [0.56 , 177.08]**	
Total events:	62		2				
Heterogeneity: Tau² = 2.99; Chi² = 2.90, df = 1 (P = 0.09); I² = 66%							
Test for overall effect: Z = 1.57 (P = 0.12)							
7.1.2 UFH							
Gurfinkel 1995	10	70	0	37	19.2%	11.24 [0.68 , 186.60]	
Subtotal (95% CI)		70		37	19.2%	**11.24 [0.68 , 186.60]**	
Total events:	10		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.69 (P = 0.09)							
7.1.3 UFH + warfarin							
Cohen 1994	7	105	3	109	32.4%	2.42 [0.64 , 9.12]	
Subtotal (95% CI)		105		109	32.4%	**2.42 [0.64 , 9.12]**	
Total events:	7		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.31 (P = 0.19)							
Total (95% CI)		989		942	100.0%	**6.80 [1.23 , 37.49]**	
Total events:	79		5				
Heterogeneity: Tau² = 1.89; Chi² = 9.05, df = 3 (P = 0.03); I² = 67%							
Test for overall effect: Z = 2.20 (P = 0.03)							
Test for subgroup differences: Chi² = 1.45, df = 2 (P = 0.49), I² = 0%							

0.01 0.1 1 10 100
Favours treatment   Favours control

Comparison 8. Incidence of thrombocytopenia over all time periods

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.1 Heparin vs placebo or untreated control	2	1717	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.24]
8.1.1 LMWH	2	1610	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.24]
8.1.2 UFH	1	107	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1.3 UFH + warfarin	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 8.1. Comparison 8: Incidence of thrombocytopenia over all time periods, Outcome 1: Heparin vs placebo or untreated control

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.1.1 LMWH							
FRISC 1996	0	746	2	760	100.0%	0.20 [0.01 , 4.24]	
Gurfinkel 1995	0	68	0	36		Not estimable	
Subtotal (95% CI)		**814**		**796**	**100.0%**	**0.20 [0.01 , 4.24]**	
Total events:	0		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.03 (P = 0.30)							
8.1.2 UFH							
Gurfinkel 1995	0	70	0	37		Not estimable	
Subtotal (95% CI)		**70**		**37**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.1.3 UFH + warfarin							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**884**		**833**	**100.0%**	**0.20 [0.01 , 4.24]**	
Total events:	0		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.03 (P = 0.30)							
Test for subgroup differences: Not applicable							

0.01 0.1 1 10 100
Favours treatment   Favours control

APPENDICES

Appendix 1. Search strategies 2014

CENTRAL on The Cochrane Library (issue 12, 2013)

#1 MeSH descriptor: [Heparin] explode all trees

#2 heparin in All Text

#3 lmwh in All Text

#4 nadroparin in All Text

#5 fraxiparin in All Text

#6 enoxaparin in All Text

#7 clexane in All Text

#8 lovenox in All Text

#9 dalteparin in All Text

#10 fragmin in All Text

#11 ardeparin in All Text

#12 normiflo in All Text

#13 tinzapain in All Text

#14 logiparin in All Text

#15 innohep in All Text

#16 certoparin in All Text

#17 sandoparin in All

#18 reviparin in All Text

#19 clivarin in All Text

#20 UFH

#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

#22 MeSH descriptor: [Acute Coronary Syndrome] this term only

#23 MeSH descriptor: [Angina, Unstable] explode all trees

#24 MeSH descriptor: [Myocardial Infarction] this term only

#25 non-Q-wave in All Text

#26 non-st-segment in All Text

#27 "without st segment" in All Text

#28 NSTEMI in All Text

#29 unstable next angina in All Text

#30 (coronary in All Text near/3 syndrome* in All Text)

#31 (unstable in All Text near/3 coronary in All Text)

#32 #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31

#33 #21 and #32 from 2001 to 2014

MEDLINE OVID

1. exp Heparin/

2. heparin.tw.

3. lmwh.tw.

4. nadroparin.tw.

5. fraxiparin.tw.

6. enoxaparin.tw.

7. clexane.tw.

8. lovenox.tw.

9. dalteparin.tw.

10. fragmin.tw.

11. ardeparin.tw.

12. normiflo.tw.

13. tinzapain.tw.

14. logiparin.tw.

15. innohep.tw.

16. certoparin.tw.

17. sandoparin.tw.

18. reviparin.tw.

19. clivarin.tw.

20. UFH.tw.

21. or/1-20

22. Acute Coronary Syndrome/

23. exp Angina, Unstable/

24. Myocardial Infarction/

25. non st segment.tw.

26. without st segment.tw.

27. non-Q-wave.tw.

28. NSTEMI.tw.

29. unstable angina.tw.

30. coronary syndrome$.tw.

31. unstable coronary.tw.

32. or/22-31

33. 21 and 32

34. randomized controlled trial.pt.

35. controlled clinical trial.pt.

36. randomized.ab.

37. placebo.ab.

38. clinical trials as topic.sh.

39. randomly.ab.

40. trial.ti.

41. 34 or 35 or 36 or 37 or 38 or 39 or 40

42. exp animals/ not humans.sh.

43. 41 not 42

44. 33 and 43

45. (2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014*).ed.

46. 44 and 45

EMBASE OVID

1. exp Heparin/

2. heparin.tw.

3. lmwh.tw.

4. nadroparin.tw.

5. fraxiparin.tw.

6. enoxaparin.tw.

7. clexane.tw.

8. lovenox.tw.

9. dalteparin.tw.

10. fragmin.tw.

11. ardeparin.tw.

12. normiflo.tw.

13. tinzapain.tw.

14. logiparin.tw.

15. innohep.tw.

16. certoparin.tw.

17. sandoparin.tw.

18. reviparin.tw.

19. clivarin.tw.

20. UFH.tw.

21. or/1-20

22. Acute Coronary Syndrome/

23. exp Angina, Unstable/

24. Myocardial Infarction/

25. non st segment.tw.

26. without st segment.tw.

27. non-Q-wave.tw.

28. NSTEMI.tw.

29. unstable angina.tw.

30. coronary syndrome$.tw.

31. unstable coronary.tw.

32. or/22-31

33. 21 and 32

34. random$.tw.

35. factorial$.tw.

36. crossover$.tw.

37. cross over$.tw.

38. cross-over$.tw.

39. placebo$.tw.

40. (doubl$ adj blind$).tw.

41. (singl$ adj blind$).tw.

42. assign$.tw.

43. allocat$.tw.

44. volunteer$.tw.

45. crossover procedure/

46. double blind procedure/

47. randomized controlled trial/

48. single blind procedure/

49. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48

50. (animal/ or nonhuman/) not human/

51. 49 not 50

52. 33 and 51

53. (2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014*).em.

54. (2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014*).dd.

55. 53 or 54

56. 52 and 55

57. limit 56 to embase

CINAHL

S39 S38 AND S37

S38 EM 2002-2014

S37 S18 AND S36

S36 S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35

S35 TX cross-over*

S34 TX crossover*

S33 TX volunteer*

S32 (MH "Crossover Design")

S31 TX allocat*

S30 TX control*

S29 TX assign*

S28 TX placebo*

S27 (MH "Placebos")

S26 TX random*

S25 TX (doubl* N1 mask*)

S24 TX (singl* N1 mask*)

S23 TX (doubl* N1 blind*)

S22 TX (singl* N1 blind*)

S21 TX (clinic* N1 trial?)

S20 PT clinical trial

S19 (MH "Clinical Trials+")

S18 S6 AND S17

S17 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16

S16 "unstable coronary"

S15 "coronary syndrome*"

S14 "unstable angina"

S13 NSTEMI

S12 "non-Q-wave" or "non Q wave"

S11 "without st segment"

S10 "non st segment"

S9 (MH "Myocardial Infarction+")

S8 (MH "Angina, Unstable")

S7 (MH "Acute Coronary Syndrome")

S6 S1 OR S2 OR S3 OR S4 OR S5

S5 sandoparin or reviparin or clivarin or UFH

S4 normiflo or tinzapain or logiparin or innohep or certoparin

S3 clexane or lovenox or dalteparin or fragmin or ardeparin

S2 heparin or lmwh or nadroparin or fraxiparin or enoxaparin

S1 (MH "Heparin+")

LILACS

heparin$ [Words] and (coronary$ OR angina$ OR myocard$) [Words]

FEEDBACK

From David Cundiff, August 2008

Summary

I thank Drs. Magee, Moher, and Rowe for completing the review.

The phenomenon of reactivation of unstable angina after the discontinuation of heparin has been described by Theroux.[1] Even when aspirin is added to heparin in patients with unstable angina, the benefit of the heparin in preventing MIs ceases after the infusion.[2-5] Rebound hypercoagulability with reactivation of angina and/or MI has not been ruled out with LMWH. If overall mortality is improved with heparins, despite the rebound hypercoagulability and reactivation of unstable angina problem and the serious bleeding risk, then using one of these drugs would be justified. However, if heparin use merely delays MIs until the withdrawal period without reducing mortality, then the additional bleeding risk would move the risk-benefit analysis toward an assessment of net harm.

Over 60% of the subjects in the 8 RCTs in this meta-analysis came from the FRISC study using dalteparin published in 1995. This RCT contains 94% of the subjects receiving LMWHs. The conclusions of this review depend entirely on this RCT. The ACC/AHA 2007 Guideline for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction states, "Dalteparin was evaluated for management of patients with UA/NSTEMI in an era before the widespread use of important therapies such as stents, clopidogrel, and GP IIb/IIIa inhibitors. Its relative efficacy and safety in the contemporary management era is not well established."[6]

In the FRISC trial, dalteparin 120 IU / kg q12 hours was given the first 6 days and then 7500 IU qd for the next 35-40 days. The incidence of death or MI in the first 6 days strongly favoured dalteparin over placebo (13/743 versus 36/759, p < 0.001). However, the event rate of deaths or MIs from days 7-14 after the reduction in dalteparin dose non significantly favoured placebo (13/724 versus 7/721, p = 0.19), suggesting a rebound effect. At 42 days into the trial just before the maintenance dose of dalteparin was stopped, the combined endpoint of deaths and MIs only marginally favoured anticoagulation (p = 0.07). At 6 months, the only data point after the dalteparin was discontinued, there was no significant difference in the combined death and MI endpoint (placebo: 116/749 versus dalteparin: 102/726, p = 0.41). Deaths were not significantly different (placebo: 41/749 versus dalteparin: 39/726). Two questions arise: (1) Are any short term benefits are off-set by later excess mortality? and (2) Are the major and fatal bleeding risks of heparins more than off-set by a significant reduction in mortality? The answer to both questions is "no." However, the short term benefit of deferring MIs until immediately after discontinuation of anticoagulation cannot justify the risk of heparins. According to a meta-analysis by Landefeld and colleagues, "The average daily frequencies of fatal, major, and major or minor bleeding during heparin therapy were 0.05%, 0.8%, and 2.0%, respectively; these frequencies are approximately twice those expected without heparin therapy."[7] For each 1 million people with ACS treated with 10-day courses of heparins, the anticoagulant would cause 2500 bleeding deaths and 40,000 major bleeds.

In conclusion, since injectable anticoagulants do not reduce either early or late mortality in acute coronary syndrome and merely delay heart attacks until immediately after the infusion, the risk of major, permanently disabling, and fatal bleeding (much greater now than when these studies were done) is not justified.

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Reply

Our research team would like to thank Dr. Cundiff for his comments on our review.

Dr. Cundiff contends that the short term benefits of heparin are not offset by later mortality and morbidity; however, we disagree. While studies included in this review reported outcome data restricted to the acute phase of interventions, nearly 17% of enrolled subjects had outcomes reported at 3 months. Dr. Cundiff is correct in pointing out that the majority of subjects in this systematic review came from the FRISC study; however, the number is in fact 48% (1498/3110) and not over 60% as he has suggested. While this systematic review was underpowered to detect a treatment difference in rare outcomes such as mortality between heparins and placebo, it did demonstrate that heparins reduced the incidence of myocardial infarction with a NNT of 33. Although there was a trend towards more major bleeds in the heparin group, this was non-significant with an actual risk difference of 0.6% between subjects treated with heparins and placebo over the course of the treatment in included studies.

We stand by our assertion that heparins appear to be a safe and effective treatment for acute coronary syndromes. Head-to-head comparisons of low molecular weight heparins with unfractionated heparin suggest that LMWHs have a decreased risk of myocardial infarction, the need for urgent revascularization and thrombocytopenia.[1] Finally, this is concordant with the most recent ACC/AHA Guidelines.[2]

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Contributors

Carlos A. Andrade-Castellanos

Luis E. Colunga-Lozano

Netzahualpilli Delgado-Figueroa

Kirk Magee

W H A T ' S   N E W

Date	Event	Description
9 February 2021	Review declared as stable	Heparin is currently the standard of care for ACS; thus, it is no longer compared with a placebo (there are no new trials that fit eligibility criteria).

H I S T O R Y

Protocol first published: Issue 1, 2002
Review first published: Issue 2, 2008

Date	Event	Description
31 March 2014	New search has been performed	Search updated to January 2014. Methodology of the review updated to incorporate 'Risk of bias' and 'Summary of findings´ tables.
8 February 2014	New citation required but conclusions have not changed	Title of the review was changed to reflect the population evaluated. New authors have taken over this review. The review was updated with nine additional excluded studies. No new studies were found for inclusion.
27 July 2010	Feedback has been incorporated	Feedback and author response added. Due to unforeseen circumstances, the feedback was not published when received in August 2008. The Cochrane Heart Group apologises for the delay
8 September 2008	Amended	Converted to new review format.
28 January 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Andrade-Castellanos CA: Editing manuscript, study selection, quality and 'Risk of bias' assessment, data entry and analysis, report writing and editing entry and analysis, report writing and editing, Current primary author.

Colunga-Lozano L: Editing manuscript, study selection, data entry and analysis.

Delgado-Figueroa N: Editing manuscript, quality and 'Risk of bias' assessment.

Magee KD: Protocol development, grant writing, study selection and quality assessment, data entry and analysis, report writing and editing entry and analysis, report writing and editing.

DECLARATIONS OF INTEREST

The authors who have been involved in this review have done so without any known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Department of Emergency Medicine, Dalhousie University, Halifax, Canada
- Department of Emergency Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada
- Thomas Chalmers Centre for Systematic Reviews, University of Ottowa, Canada
- Department of Internal Medicine, Hospital Civil de Guadalajara "Dr. Juan I. Menchaca", Mexico

  (Internal support for the update)

External sources

- Canada Institute of Health Research (CIHR), Ottawa, Ontario, Canada

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As acknowledged, in 2014 our group was granted to continue and prepare the review. The published protocol originally prepared by Magge et al dates back to 2002. During the update process, the title of the review changed from *Heparin versus placebo for acute coronary syndromes (ACS)* to *Heparin versus placebo in non-ST elevation acute coronary syndromes (NSTEACS)* in order to reflect the population evaluated.

In the words of Kirk Magee, STEMI patients were excluded from this review because it was felt that patients with STEMI categorically differed from patients with unstable angina/NSTEMI with respect to their presentation, underlying pathophysiology and treatment. Clinically,

patients with STEMI are different than patients with unstable angina/NSTEMI Including patients with STEMI would introduce significant heterogeneity in the results and would not allow for the performance of a meta-analysis. Also, when the review was first published, the term ACS was inclusive of unstable angina/NSTEMI and did not include STEMI.

We take the rationale of Kirk Magee as our own. However, in order to avoid misleading conclusions regarding the diversity of patients with ACS, we, in agreement with Kirk Magee, decided to change the title of this Cochrane review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Coronary Syndrome [*drug therapy] [mortality]; Angina, Unstable [drug therapy]; Anticoagulants [adverse effects] [*therapeutic use]; Heparin [adverse effects] [*therapeutic use]; Heparin, Low-Molecular-Weight [adverse effects] [therapeutic use]; Myocardial Infarction [prevention & control]; Placebos [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans