Heparin versus placebo for acute coronary syndromes (Review)

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[Intervention Review]

Heparin versus placebo for acute coronary syndromes

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ABSTRACT

Background

Acute coronary syndromes (ACS) represent a spectrum of disease including unstable angina (UA) and non-ST segment myocardial infarction (NSTEMI). Despite treatment with aspirin, beta-blockers and nitroglycerin, UA/NSTEMI is still associated with significant morbidity and mortality. Although emerging 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 ACS.

Objectives

To determine the effect of heparins (UFH and LMWH) compared with placebo for the treatment of patients with ACS.

Search methods

We searched the Cochrane Central Register of Controlled Trials on *The Cochrane Library* (issue 4, 2002), MEDLINE (1966 to May 2002), EMBASE (1980 to May 2002) and CINAHL (1982 to May 2002). Authors of included studies and pharmaceutical industry representatives were contacted to determine if unpublished studies which met the inclusion criteria were available.

Selection criteria

Randomized controlled trials of parenteral UFH or LMWH versus placebo in people with ACS (UA or NSTEMI).

Data collection and analysis

Two reviewers independently assessed quality of studies. Data were extracted independently by two reviewers. Study authors were contacted to verify and clarify missing data.

Main results

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 (RR = 0.84, 95% CI 0.36 to 1.98). Heparins reduced the occurrence of MI (RR = 0.40, 95% CI 0.25 to 0.63, NNT = 33). An increase in the incidence of minor bleeds (RR = 6.80, 95% CI 1.23 to 37.49, NNH = 17).

Authors' conclusions

Compared to placebo, patients treated with heparins had similar risk of mortality, revascularization, recurrent angina, major bleeding and thrombocytopenia. However, those treated with heparins had decreased risk of MI and a higher incidence of minor bleeding.

PLAIN LANGUAGE SUMMARY

Heparins reduce the number of heart attacks but caused more minor bleeding after acute coronary syndromes compared to 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.

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). Acute coronary syndromes are characterized by the formation of atherolsclerotics plaque. Plaque disruption or erosion is the final step in the activation of the platelet system and the coagulation cascade in the coronary vessels. The resulting labile thrombus causes a transient occlusion of the coronary arteries resulting in the clinical presentation of unstable angina (Fuster 1995). Recent research has highlighted the increasingly central role of inflammation in the pathogenesis of atherosclersosis. 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 reperfussion therapy with systemic fibrinolytic therapy or immediate percutaneous coronary intervention.

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 pentasaccaride 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 deploymerization of standard UFH into lower molecular weight fragments has a number of theoretical advantages including a more predicatable 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).

Although a recent systematic review has shown a trend towards improved efficacy with the addition of UFH to aspirin therapy (Oler 1996), this study failed to show a significant reduction in death and myocardial infarction. Despite this, UFH is considered the accepted treatment standard for NSTEMI and unstable angina (RISC 1990; Theroux 1988) and continues to be the benchmark against which LMWH and other agents are judged.

With the advent of LMWH and other agents such as IIb/IIIa platelet inhibitors, there is renewed interest in the role of heparin in the treatment of acute coronary syndromes. Although emerging evidence suggests that LMWH is more efficacious compared to UFH (Eikelboom 2000; Magee 2003), there is limited data to support the role of heparin as a drug class in the treatment of acute coronary syndromes. This systematic review of heparins (UFH and

LMWH) in the acute treatment of unstable angina and NSTEMI attempts to fill that void.

OBJECTIVES

The objective of this systematic review was to determine the effect of heparin compared with placebo for the treatment of patients with 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 which included adult patients (> 18 years of age) presenting with acute coronary syndromes requiring treatment within 72 hours of presentation of their last episode of chest pain were considered eligible for inclusion. 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 standard aspirin therapy and be randomized to receive treatment with either parentral UFH of LMWH compared to placebo within 72 hours of presentation.

Types of outcome measures

Only studies reporting clinically relevant outcomes were considered. Outcomes over all time periods were considered. Outcomes included:
- death (all cause mortality);
- myocardial infarction;
- 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);
- major hemorrhage (e.g. fall in hemoglobin level of >20 g/L, requires transfussion, is intracranial, retroperitoneal, or intraocular, or causes death or ceasation of the study treatment);
- minor hemorrhage (e.g. any clinically important bleed that does not qualify as major; e.g. epistaxis, ecchymosis or hematoma, or macroscopic hematuria);
- thrombocytopenia (e.g. platelet count $<100x10^9$/L);
- allergic reactions.

Search methods for identification of studies

Comprehensive searches of the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (Issue 4, 2002), MEDLINE (January 1966 to May 2002), EMBASE (1980 to May 2002) and CINAHL (1982 to May 2002) were completed. There were no language or publication status restrictions. The search consisted of the following terms:
a) heparin OR low molecular weight heparin OR LMWH OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzapain OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin AND
b) angina OR angina pectoris OR non-Q-wave myocardial infarction
Reference lists of all available primary studies and review articles were reviewed to identify potential relevant citations. Inquiries regarding other published or unpublished studies known and/or supported by the authors of the primary studies were made so that these results could be included in this review. Scientific advisors of the various pharmaceutical companies (Aventis, Leo, Novartis, Pharmacia, Sanofi-Synthelabo, Wyeth-Ayerst) that manufacture LMWH were contacted for any unpublished or interim results on the acute use of LMWH for patients with unstable angina. Finally, personal contact with colleagues, collaborators and other trialists working in the field of acute coronary syndromes was made to identify potentially relevant studies.

Data collection and analysis

Retrieval of studies

All trials which appeared relevant on the basis of title, abstract, and MeSH headings were selected for full review by two reviewers (KM and BR or SC).
From these potentially relevant articles, and any added from the grey literature searches or communication, two reviewers (KM, BR) independently selected trials (based on the full text format) for inclusion in this review. Agreement was measured using simple agreement and kappa statistics. Disagreement was resolved by consensus or third party adjudication. Independent reviewers (KM, BR) extracted the data of each included study.

Assessment of methodological quality

The methodological quality assessment was performed using two methods and independently by two reviewers. The abstractors were not blinded to the authors or the results of the study; however, we performed a pilot study of the two methods of quality assessment, followed by an observer reliability study. An acceptable level of agreement was reached on the first pilot in order for the quality assessment approach to be considered acceptable (kappa = 0.61). Using the Cochrane approach to assessment of allocation concealment (Clarke 2001), all trials were scored and entered using the following principles: (A) adequate; (B) uncertain; (C) inadequate; (D) not used. Inter-rater reliability was measured by using kappa weighted statistics. In addition, each study was assessed using a 0-5 validated scale described by Jadad (Jadad 1996).

Data extraction

Data for the trials were extracted independently by two reviewers (BR, KM) and entered into Review Manager software. Data extraction included the following items:

- Population: age, gender, time to presentation, inclusion and exclusion criteria;
- Intervention: agent, dose, duration of therapy;
- Control: UFH dose, weight-based versus fixed dosing, duration, target aPTT, time to adequate aPTT;
- 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.

The data were also evaluated for the presence of publication bias using graphical and statistical methods.

Statistical considerations

An analysis was completed which deals with the 'missing data' issues from the individual trials. If a publication bias was present, the results were adjusted using the Egger approach and the 'trim and fill' approach (Egger 1997). In addition, quality weighting was used to test the robustness of the results.
All trials were combined using the Review Manager (Update Software, Version 4.2.7; Oxford, UK). For dichotomous variables, individual and pooled statistics were calculated as relative risks (RR) with 95% confidence intervals (95% CI). A random-effects model was used when more than five trials were pooled. When fewer trials or no heterogeneity was identified, a fixed-effect model was employed. For continuous outcomes, individual and pooled statistics were calculated as weighted mean differences (WMD) or standardized mean differences (SMD) and 95% CIs using a random-effects model. Heterogeneity was assessed using the I^2 statistic(Higgins 2003). The presence of publication bias was examined visually using a funnel plot.

Subgroup analysis

Two specific subgroups were planned *a priori*:
a) Population: unstable angina vs. unstable angina and NSTEMI; and
b) Intervention: UFH versus LMWH.

Sensitivity analysis

In the setting of significant heterogeneity ($P < 0.1$), *a priori* we decided the groups would be divided using the following criteria:
a) Methodological quality: those studies with a Jadad score of 3 or higher versus those with a score of less than 3.
b) Statistical sensitivity (FE vs. RE).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
The computerized search of EMBASE, MEDLINE and CINAHL identified 2193 original publication citations. Independent review of the abstracts and titles of these publications identified 56 potentially relevant studies (k = 0.38). Of these potentially relevant articles, eight studies met inclusion critetria, with a total of 3118 patients being included in this systematic review. The kappa statistic for inter-rater agreement on including or excluding potential trials was 'substantial' (k = 0.83) (Landis 1977). One potentially relevant abstract is awaiting assessment as detailed methodology and outcomes could not be obtained (Zwerner 1987). The full list of excluded studies and reasons for exclusion are given in the Characteristics of excluded studies table.
The evidence for the use of heparins in acute coronary syndrome first appeared in the literature in the late 1980s with studies

comparing heparin versus aspirin or non-aspirin controls. By the mid 1990s, studies began replacing UFH with LMWH (Cohen 1990; Cohen 1994; Doucet 2000; FRISC 1996; Gurfinkel 1995; Holdright 1994; RISC 1990; Theroux 1988). With the exception of the two Swedish trials that enrolled nearly 1500 patients (FRISC 1996) and over 900 patients (RISC 1990), the remaining six studies were smaller, enrolling less than 400 patients each. Two studies were conducted in Canada (Doucet 2000; Theroux 1988), one in the United Kingdom (Holdright 1994), one in the United States (Cohen 1994) and one in Argentina (Gurfinkel 1995). Additionally, one study (Cohen 1994) was conducted in both the United Kingdom and the United States.

Study design

All studies were RCTs; however, not all were double blind. In three studies (Doucet 2000; FRISC 1996; Theroux 1988), concealment of allocation was adequate. In the remaining studies, there was insufficient evidence to determine whether or not there was adequate concealment. 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 for 5 to 7 months. In all other studies, however, the patients were followed and the outcomes measured at 3 months.

Participants

Traditionally, heparin was started in the treatment of acute coronary syndromes based on history alone; however, in many of these studies, patients were selected on the basis of more 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 2 weeks to 6 months following coronary angioplasty.

Interventions

The studies were conducted over an 11-year time period from 1985 until 1996 and included 3110 patients treated with either UFH or LMWH. In total, 1602 patients (52%) were eligible to receive LMWH and 1508 patients (48%) were eligible to receive UFH. Two different LMWHs were used: dalteparin (1498 eligible subjects) and nadroparin (104 eligible subjects). Of the patients receiving UFH, 19% were switched to warfarin when the UFH was discontinued. Most trials mandated that subjects receive 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 2 to 7 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.

Outcomes

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, and are similar to the outcomes reported in the Cochrane review on UFH versus LMWH in the treatment of acute coronary syndromes (Magee 2003). 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 developement 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; Theroux 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 3 months. In four studies, endpoints were recorded over a 5 to 8 day period (Doucet 2000; FRISC 1996; Gurfinkel 1995; Holdright 1994), while in the other four studies, end points were measured at 3 months (Cohen 1990; Cohen 1994; RISC 1990; Theroux 1988). We have grouped the results for all reported time periods.

Risk of bias in included studies

Using the Jadad method, four studies representing 75% of enrolled subjects, were rated as methodologically 'high quality' (Doucet 2000; FRISC 1996; RISC 1990; Theroux 1988) and four were rated as 'weak' (Cohen 1990; Cohen 1994; Gurfinkel 1995; Holdright 1994). The median score was 3 with an interquartile

range of 2 to 4. Using the Cochrane methodology, four of the eight studies had unclear concealment of allocation.

Effects of interventions

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

Death

Death was reported as an outcome in six trials involving 2426 patients. The incidence of death in those treated with placebo was 0.9%(11/1188) compared to 0.7% (9/1238) in those treated with a heparin. Overall, there was a trend towards fewer deaths in the heparin group compared to the placebo group; however, this was not statistically significant (RR = 0.84, 95% CI 0.36 to 1.98, P = 0.82, I2 = 0%).

Myocardial infarction

Myocardial infarction was reported as an outcome in six trials involving 2426 patients. 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 MI 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.

Recurrent angina

Recurrent angina was reported as an outcome in six studies involving 2426 patients. 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%). The subgroup of LMWH demonstrated a clear benefit compared to aspirin alone, consistent with the previous acute coronary syndromes review on this topic (Magee 2003).

Revascularization procedures

The need for a revascularization procedure was reported as an outcome in six of the eight included studies involving 2520 patients. 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%).

Multiple end points

We were able to calculate the incidence of death **or** myocardial infarction for all eight included studies involving a total of 3110 patients. 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.

Major bleeds

Eight trials, involving 3118 patients, reported major bleeds as an outcome. There was a trend towards more major bleeds in the heparin studies compared to control studies; however, this did not reach the required level of statistical significance (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, but this was not statistically significant (RR = 7.26, 95% CI 0.38 to 138). No heterogeneity was observed in this outcome (P = 0.93).

Minor bleeds

Only three of the eight included studies (n = 1931) reported minor bleeds as an outcome. 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.

Thrombocytopenia

Only two studies (n = 1717) reported the outcome of thrombocytopenia. 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%).

Sensitivity analysis

Sensitivity analysis based on random-effects versus fixed-effect modelling 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 subjects. 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 UA 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 = 0.0087 and I^2 = 66.6%) and revascularization procedures (P = 0.12 and I^2 = 41.1%). 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 acute coronary syndromes and identified several important outcomes related to 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 subjects 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.

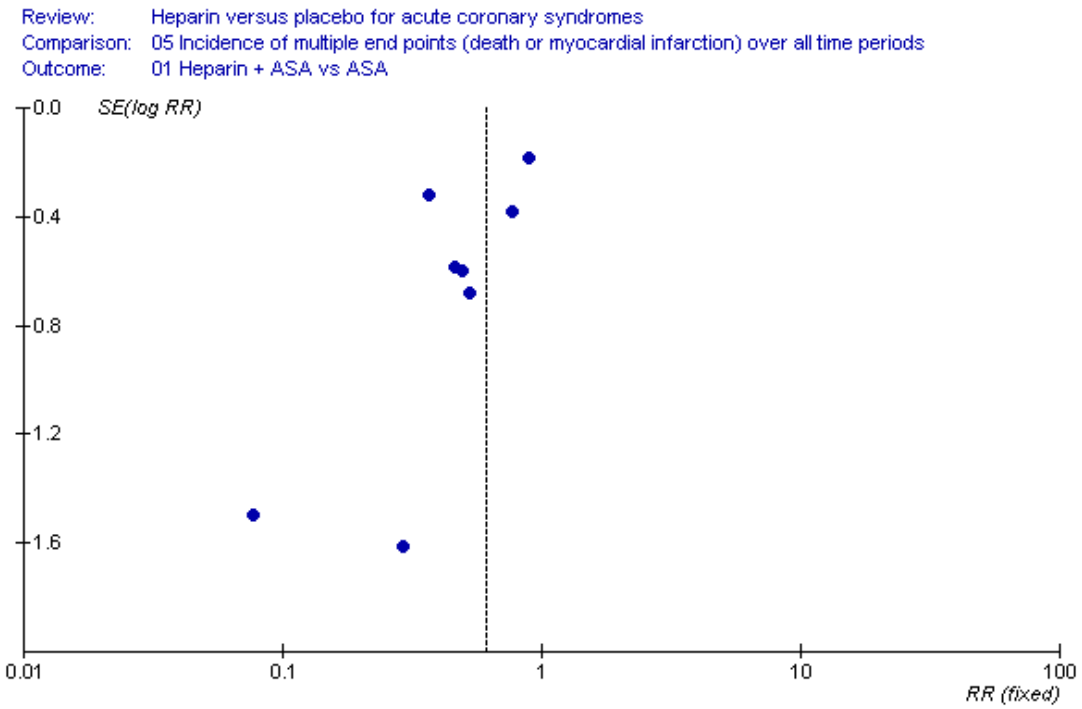
Overall, little heterogeneity was identified in the pooled results reported in this review. This is not surprising given that acute coronary syndromes represent a well-defined disease spectrum with fairly clear-cut dichotomous outcomes. Outcomes in which heterogeneity was identified included the incidence of recurrent angina and minor bleeds (I^2 = 66.6% and 66.9%, respectively). A moderate degree of heterogeneity was identified (I^2 = 41.1%) in the incidence of revascularization procedures. This can in part be accounted for by subtle differences in study design: inclusion criteria, dosing regime, 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 acute coronary syndromes. Although there were 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 (Figure 1). 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. Five 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; Theroux 1993) because of the well-accepted treatment of acute coronary syndromes with aspirin (Lewis 1983; Oler 1996; Theroux 1988). However, we employed two independent reviewers, 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.

Figure 1. Funnel plot of included studies



This systematic review illustrates the potential benefit of using heparins in the early of treatment of ACS. Patients presenting with high risk unstable angina or NSTEMI should be considered for a 5 to 8 day course of heparin therapy in addition to aspirin and standard anti-anginal therapy when they meet the criteria outlined in these studies. Most studies restricted enrolment 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. Therefore, we cannot recommend the indiscriminate use of heparins for acute coronary syndromes. UFH or LMWH must be reserved for those patients with either NSTEMI or high risk unstable angina as defined above. Finally, in those centers with active primary cardiac catheterization facilities, intravenous UFH may represent a safer option than LMWH, as it has a much shorter half-life and is more easily reversed.

In those centers with active primary cardiac catheterization facilities utilizing an early percutaneous coronary intervention (PCI) strategy, intravenous UFH may represent a safer option than LMWH, as it has a much shorter half-life and is more easily reversed. In addition, newer therapeutic options such as glycoprotein

IIb/IIIa inhibitors and clopidogrel must be considered in hospitals using an early invasive strategy for patients with UA/NSTEMI. These results are concordant with the most current recommendations made by the American Heart Association (ACLS 2000; Braunwald 2000) and similar to two previous reviews (Eikelboom 2000; Oler 1996). The AHA suggests using either LMWH or UFH for patients with intermediate to high risk unstable angina or NSTEMI. Although in our subgroup analysis, only LMWH appeared to be statistically superior to aspirin alone, there was a relatively small reduction in the absolute risk.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review of randomized controlled trials supports the use of heparins in the early treatment of 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 yet 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 2 to 8 day period, with most studies administering it for 2 to 7 days. The small number of studies makes it impossible to recommend a particular dosing regimen. As a subgroup, LMWH and not UFH was the only group to show a statistically significant improvement in any of the outcomes. LMWH reduced the incidence of myocardial infarction, recurrent angina and the need for revascularization procedures. Given the advantages of LMWH over UFH demonstrated in a previous review (Magee 2003) and the evidence reported here, LMWH should be the agent of choice in the early treatment of unstable angina and NSTEMI. In those institutions which have active primary angioplasty suites, there is limited data to recommend LMWH over UFH. Available evidence suggests that both therapies are safe and efficacious although the two treatments have not been directly compared (Wong 2003).

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 reamins an interesting, yet unresolved, question.

- With the advent of the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndrome, studies are required to determine the efficacy and safety of their use in combination with heparins.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Cohen 1990

Methods	Prospective, randomized, multicentre trial.
Participants	Patients between 21 and 75 years with unstable angina or non-Q-wave MI with last episode of pain within 48 hours of screening
Interventions	Therapy for 12 weeks (3-4 days with UFH). Group 1: ASA 325 mg/d; Group 2: UFH 100 IU/kg iv then infusion to maintain aPTT 2-3 x control for 3-4 days. Warfarin started to INR 3.0-4.5 and UFH discontinued; Group 3: ASA 325 mg/d + UFH 100 IU/kg iv then infusion to maintain aPTT 2-3 x control for 3-4 days. Warfarin started to INR 3.0-4.5 and UFH discontinued
Outcomes	Outcomes at 12 weeks.
Notes	ASA vs ASA + UFH/warfarin. Use data from group 1 and 3 only.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Cohen 1994

Methods	Prospective, randomized, multicentre trial.
Participants	Patients over 21 years with unstable angina or non-Q-wave MI with last episode of pain within 48 hours of randomization
Interventions	Therapy for 12 weeks (3-4 days with UFH) . Group 1: ASA 162.5 mg/d; Group 2: ASA 162.5 mg/d + UFH 100 IU/kg bolus iv then infusion. Warfarin to be started on day 3 or 4 to maintain INR 2 to 3
Outcomes	Outcomes at hospital discharge and every 3 weeks until 12 weeks
Notes	ASA vs ASA + UFH/warfarin.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Doucet 2000

Methods	Prospective, 2x2 factorial double-blind, placebo-controlled, randomized trial
Participants	All patients with unstable angina within 2 weeks to 6 months after coronary angioplasty occuring within 24 hours of randomization
Interventions	Therapy started within 24 hrs. Therapy for 48-96 hours. All grougps receive ASA 325 mg/d. Group 1: iv NTG + placebo UFH; Group 2: placebo + iv UFH; Group 3: iv NTG + iv UFH; Group 4: placebo + placebo
Outcomes	Outcomes at 58-96 hours. Death, MI, recurrent angina, bleeding complications
Notes	Unstable angina defined by symptoms and ECG changes. In abscence of ECG changes, independent confirmation by 2 cardiologists. For this review, groups 1+4 and 2+3 were combined to make two separate groups

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

FRISC 1996

Methods	Prosepective, multicentre, double-blind, randomized, placebo-controlled, parallel-group trial
Participants	All men over 40 years and women at least 1 year after menopause admitted to hospital with chest pain within the previous 72 hours
Interventions	Therapy started within 72 hours. Group 1: dalteparin 120 IU/kg sc bid x 6 days. Group 2: placebo. All patients recieved ASA 300 mg then 75 mg OD, beta-blocker and/or calcium channel blockers/nitrates
Outcomes	Acute phase: 5-8 days in hospital. Home treatment phase: 35-45 days. Outcomes included death, MI, recurrent angina, urgent revascularization, major/minor heomorrhage, and thrombocytopenia
Notes	Only use data from first 6 days (exclude home LMWH therapy).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gurfinkel 1995

Methods	Prospective, randomized, single-blind trial.
Participants	All patients greater than 21 years with ustable angina within 24 hours of randomization
Interventions	Therapy for 5-7 days. Group 1: ASA 200 mg/d + UFH placebo; Group 2: ASA 200 mg/d + UFH 5000 IU iv then 400 IU/kg/d; Group 3: ASA + nadroparin 214[UIC]/kg anti-Xa sc bid + UFH placebo
Outcomes	Over 5 to 7 days. Death, MI, recurrent angina, urgent revascularization, silent ischemia, major/minor heomorrhage, and thrombocytopenia
Notes	Split control group.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Holdright 1994

Methods	Prospective, randomized, single-blind multicentre trial.
Participants	All patients 30 to 75 years with a diagnosis of unstable angina
Interventions	Therapy for 2 days started within 24 hours of chest pain. Group1: ASA 150 mg/d; Group 2: ASA 150 mg/d + UFH 5000 IU iv then infusion to maintain aPTT 1.5-2.5 x baseline
Outcomes	Outcomes over the duration of the hospital admission.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

RISC 1990

Methods	Prosepective, randomized, double blind, placebo-controlled multicentre trial
Participants	All men below 70 yrs with symptoms suggesting unstable CAD.
Interventions	Therapy for 5 days . Randomised to treatment up to 72 hours after admission. Group 1: ASA placebo + UFH placebo; Group 2: ASA placebo + UFH 5000 IU iv qid x 1 day then UFH 3750 IU iv qid x 4 days; Group 3: ASA 75 mg/d + UFH placebo; Group 4: ASA 75 mg/d + UFH 5000 IU iv qid x 1 day then UFH 3750 IU iv qid x 4 days

RISC 1990 (*Continued*)

Outcomes	Outcomes at 5 days, 30 days and 90 days.	
Notes	Only use data from groups 3 and 4.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Theroux 1988

Methods	Double-blind, randomized trial.	
Participants	All patients who were admitted with a diagnosis of unstable angina or who acquired unstable angina while hospitalized. Most recent chest pain within 24 hours of randomization	
Interventions	Therapy for ~ 6 days. Group 1: ASA 650 mg then 325 mg bid + placebo bolus and infusion; Group 2: UFH 5000 IU iv then 1000 IU/h + placebo ASA; Group 3: ASA 650 mg then 325 mg bid + UFH 5000 IU iv then 1000 IU/h; Group 4: placebo ASA + placebo UFH	
Outcomes	Outcomes at ~ 6 days and 3 months.	
Notes	Study was discontinued prematurely on the basis of first interim data analysis. Use only data from Groups 1 and 3	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

ASA - aspirin
MI - myocardial infarction
UFH - unfractionated heparin
LMWH - low molecular weight heparin
INR - international normalized ratio
NTG - nitroglycerin

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 control trial
Borja 2000a	Not a randomized control trial
Borja 2000b	Not a randomized control trial
Borja 2000c	Not a randomized control trial
Charvat 1989	Not all patients treated with ASA
Cohen 1993	Unclear from results to which study group subjects had been randomised. Attempts to communicate with authors unsuccessful
Collins 1996	Not a randomized control trial
Correia 1995	Patients not compared to placebo
Emerg Med 1989	Not a randomized control trial
FAMI 2000	No control group in the acute phase of the study
Ferguson 1999	Not a randomized control 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 myocardial infarction
Gorski 1993	Not a randomized control trial
Goy 1999	Not a randomized control trial
Gulba 1992	Not a randomized control trial
Hasselblad 1998	Not a randomized control trial
Huber 1989	Not all patients treated with ASA
Hurtado 1984	Patients had ST-segment elevation MI
Jaffrani 1993	Not a randomized control trial

(*Continued*)

Kaul 2000	Not a randomized control trial
Kontny 2001	Not a randomized control trial
Mattioli 1999	Heparin not compared versus placebo
Milonig-Ganner 1989	Not a randomized control trial
Moise 1994	Not a randomized control trial
Montgomery 1995	Not a randomized control trial
Nardelli 1991	Not a randomized control trial
Ocampo 1998	Heparin not compared versus placebo
Oler 1996	Not a randomized control trial
PURSUIT 2001	Not the study question
Raschke 1993	Not the study question
Rubio-Terres 2001	Not a randomized control trial
Sayen 1982	Not a randomized control 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 control trial
TETAMI 2000	Not a randomized control trial
Theroux 1993	Not all patients treated with ASA
Thieuleux 1985	Not a randomized control trial
Umans 1997	Not a randomized control trial
Violaris 1991	Not a randomized control trial
Wallentin 1997	Not a randomized control trial
Wallis 1991	Not a randomized control trial

ASA - aspirin

DATA AND ANALYSES

Comparison 1. Incidence of death over all time periods

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heparin + ASA vs ASA	6	2426	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.36, 1.98]
1.1 LMWH	2	1602	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.33, 2.45]
1.2 UFH	3	541	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.04]
1.3 UFH + warfarin	2	283	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.15, 7.24]

Comparison 2. Incidence of MI over all time periods

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heparin + ASA vs ASA	6	2426	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.25, 0.63]
1.1 LMWH	2	1602	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.14, 0.55]
1.2 UFH	3	541	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.23, 1.34]
1.3 UFH + warfarin	2	283	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.25, 1.62]

Comparison 3. Incidence of recurrent angina over all time periods

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heparin + ASA vs ASA	6	2426	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.60, 1.09]
1.1 LMWH	2	1602	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.36, 0.74]
1.2 UFH	3	541	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.78, 1.24]
1.3 UFH + warfarin	2	283	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.45, 1.87]

Comparison 4. Incidence of revascularization procedures over all time periods

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heparin + ASA vs ASA	6	2520	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.76, 1.15]
1.1 LMWH	2	1602	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.09, 0.78]
1.2 UFH	3	635	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.76, 1.25]
1.3 UFH + warfarin	2	283	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.75, 1.74]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heparin + ASA vs ASA	8	3110	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.47, 0.80]
1.1 LMWH	2	1602	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.18, 0.61]
1.2 UFH	5	1225	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.58, 1.08]
1.3 UFH + warfarin	2	283	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.15, 1.28]

Comparison 6. Incidence of major bleeds over all time periods

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heparin + ASA vs ASA	8	3118	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.91, 4.60]
1.1 LMWH	2	1610	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.43, 5.39]
1.2 UFH	5	1225	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [0.59, 6.26]
1.3 UFH + warfarin	2	283	Risk Ratio (M-H, Fixed, 95% CI)	7.26 [0.38, 138.95]

Comparison 7. Incidence of minor bleeds over all time periods

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heparin + ASA vs ASA	3	1931	Risk Ratio (M-H, Random, 95% CI)	6.80 [1.23, 37.49]
1.1 LMWH	2	1610	Risk Ratio (M-H, Random, 95% CI)	9.96 [0.56, 177.08]
1.2 UFH	1	107	Risk Ratio (M-H, Random, 95% CI)	11.24 [0.68, 186.60]
1.3 UFH + warfarin	1	214	Risk Ratio (M-H, Random, 95% CI)	2.42 [0.64, 9.12]

Comparison 8. Incidence of thrombocytopenia over all time periods

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heparin + ASA vs ASA	2	1717	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.24]
1.1 LMWH	2	1610	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.24]
1.2 UFH	1	107	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 UFH + warfarin	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Incidence of death over all time periods, Outcome 1 Heparin + ASA vs ASA.

Review: Heparin versus placebo for acute coronary syndromes

Comparison: 1 Incidence of death over all time periods

Outcome: 1 Heparin + ASA vs ASA

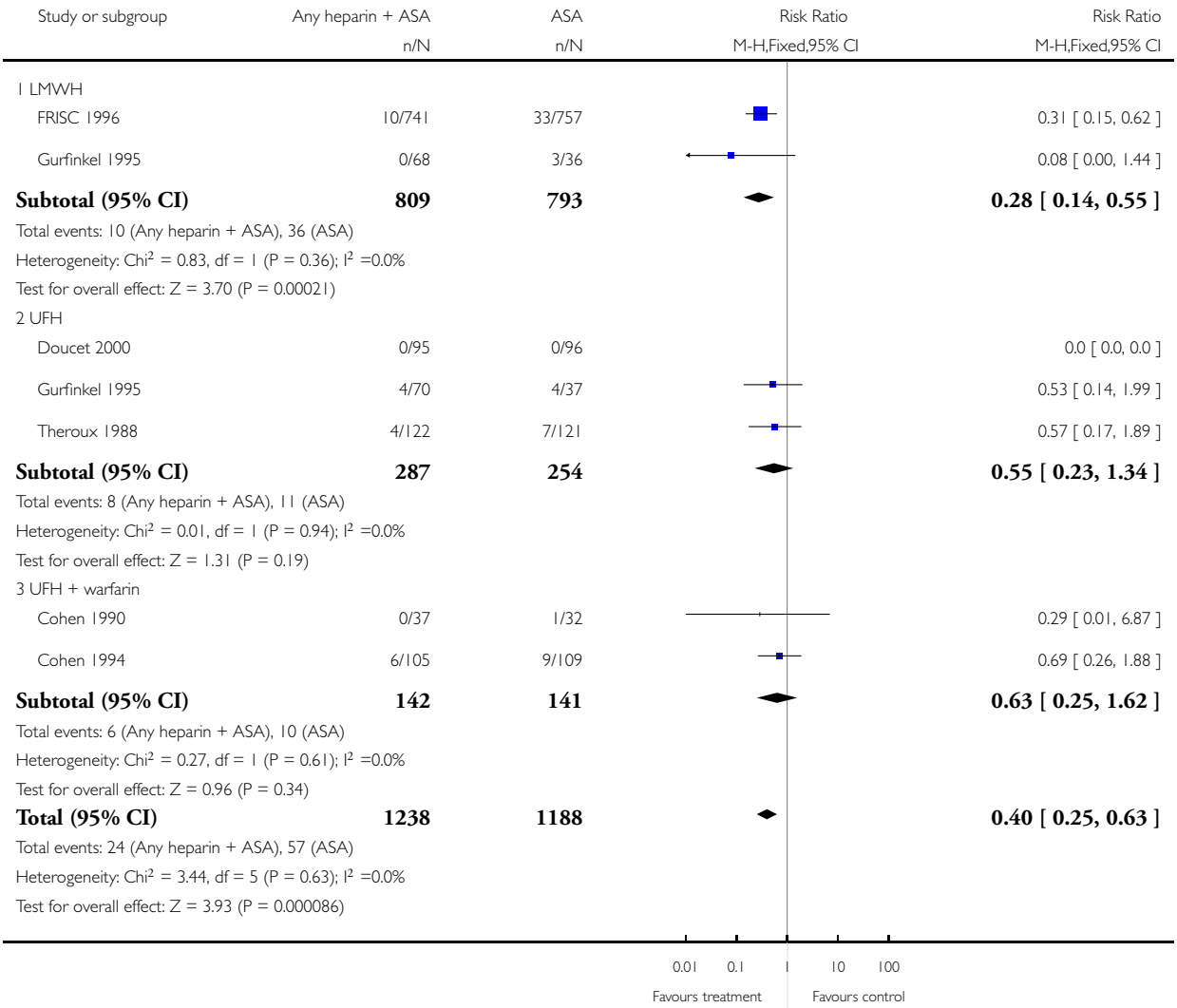
Study or subgroup	Any heparin + ASA n/N	ASA n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 LMWH				
FRISC 1996	7/741	8/757		0.89 [0.33, 2.45]
Gurfinkel 1995	0/68	0/36		0.0 [0.0, 0.0]
Subtotal (95% CI)	**809**	**793**		**0.89 [0.33, 2.45]**
Total events: 7 (Any heparin + ASA), 8 (ASA)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.22 (P = 0.83)				
2 UFH				
Doucet 2000	0/95	0/96		0.0 [0.0, 0.0]
Gurfinkel 1995	0/70	0/37		0.0 [0.0, 0.0]
Theroux 1988	0/122	1/121		0.33 [0.01, 8.04]
Subtotal (95% CI)	**287**	**254**		**0.33 [0.01, 8.04]**
Total events: 0 (Any heparin + ASA), 1 (ASA)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.68 (P = 0.50)				
3 UFH + warfarin				
Cohen 1990	0/37	0/32		0.0 [0.0, 0.0]
Cohen 1994	2/105	2/109		1.04 [0.15, 7.24]
Subtotal (95% CI)	**142**	**141**		**1.04 [0.15, 7.24]**
Total events: 2 (Any heparin + ASA), 2 (ASA)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.04 (P = 0.97)				
Total (95% CI)	**1238**	**1188**		**0.84 [0.36, 1.98]**
Total events: 9 (Any heparin + ASA), 11 (ASA)				
Heterogeneity: Chi^2 = 0.39, df = 2 (P = 0.82); I^2 =0.0%				
Test for overall effect: Z = 0.39 (P = 0.70)				

Analysis 2.1. Comparison 2 Incidence of MI over all time periods, Outcome 1 Heparin + ASA vs ASA.

Review: Heparin versus placebo for acute coronary syndromes

Comparison: 2 Incidence of MI over all time periods

Outcome: 1 Heparin + ASA vs ASA



Analysis 3.1. Comparison 3 Incidence of recurrent angina over all time periods, Outcome 1 Heparin + ASA vs ASA.

Review: Heparin versus placebo for acute coronary syndromes

Comparison: 3 Incidence of recurrent angina over all time periods

Outcome: 1 Heparin + ASA vs ASA

Study or subgroup	Any heparin + ASA n/N	ASA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Any heparin + ASA), 71 (ASA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.14$, df = 1 (P = 0.71); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.58 (P = 0.00035)					
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]
Theroux 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 (Any heparin + ASA), 90 (ASA)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.22$, df = 2 (P = 0.33); $I^2 = 10\%$					
Test for overall effect: Z = 0.11 (P = 0.91)					
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 (Any heparin + ASA), 36 (ASA)					
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 3.28$, df = 1 (P = 0.07); $I^2 = 70\%$					
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 (Any heparin + ASA), 197 (ASA)					
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 17.16$, df = 6 (P = 0.01); $I^2 = 65\%$					
Test for overall effect: Z = 1.41 (P = 0.16)					

Analysis 4.1. Comparison 4 Incidence of revascularization procedures over all time periods, Outcome 1 Heparin + ASA vs ASA.

Review: Heparin versus placebo for acute coronary syndromes

Comparison: 4 Incidence of revascularization procedures over all time periods

Outcome: 1 Heparin + ASA vs ASA

Study or subgroup	Any heparin + ASA n/N	ASA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
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 (Any heparin + ASA), 13 (ASA)					
Heterogeneity: Chi^2 = 0.54, df = 1 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 2.40 (P = 0.017)					
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]
Theroux 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 (Any heparin + ASA), 77 (ASA)					
Heterogeneity: Chi^2 = 0.35, df = 2 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 0.19 (P = 0.85)					
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 (Any heparin + ASA), 28 (ASA)					
Heterogeneity: Chi^2 = 2.68, df = 1 (P = 0.10); I^2 =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 (Any heparin + ASA), 118 (ASA)					
Heterogeneity: Chi^2 = 10.18, df = 6 (P = 0.12); I^2 =41%					
Test for overall effect: Z = 0.65 (P = 0.51)					

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

Review: Heparin versus placebo for acute coronary syndromes

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

Outcome: 1 Heparin + ASA vs ASA

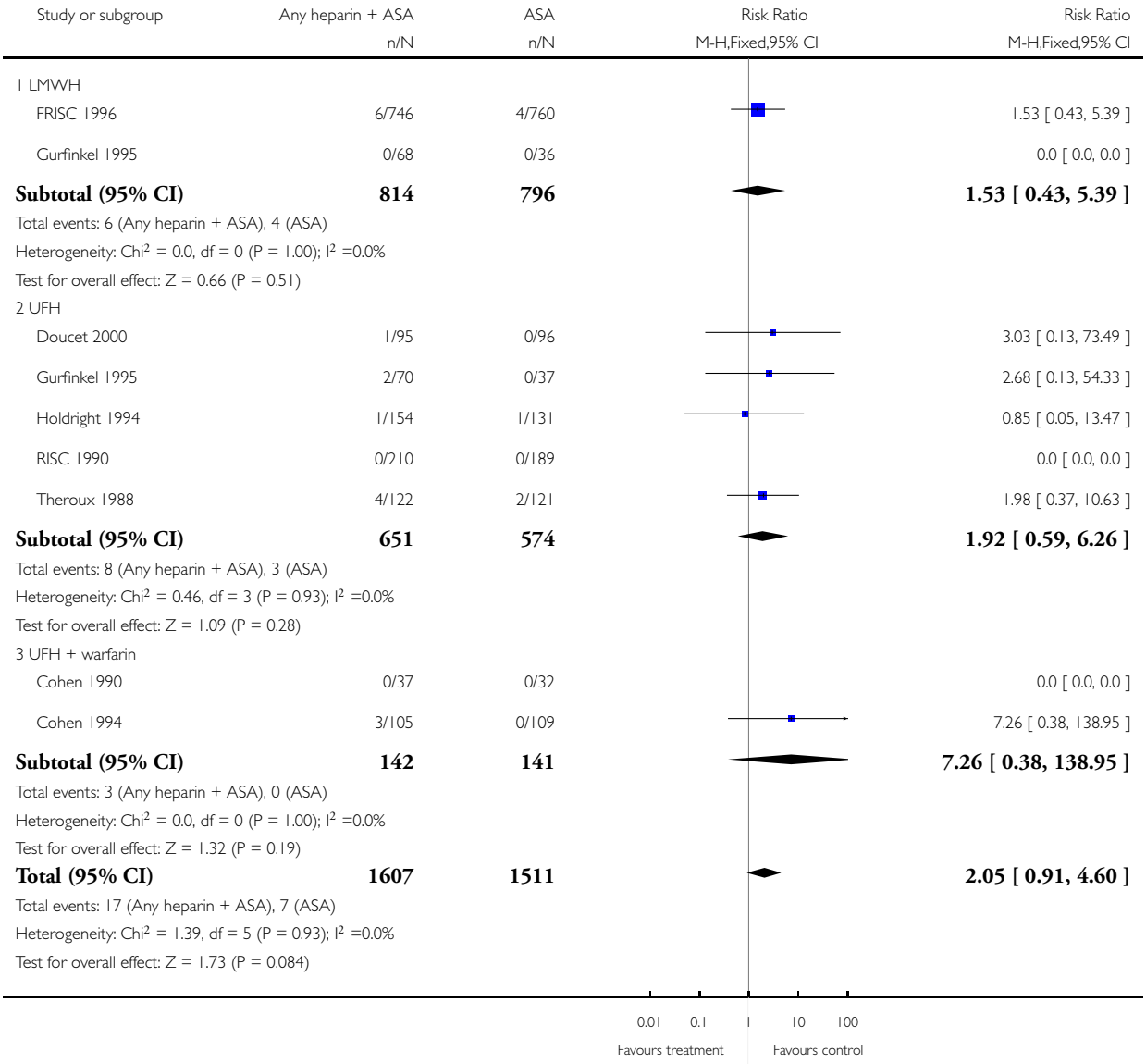
Study or subgroup	Any heparin + ASA n/N	ASA n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 LMWH				
FRISC 1996	13/741	36/757		0.37 [0.20, 0.69]
Gurfinkel 1995	0/68	3/36		0.08 [0.00, 1.44]
Subtotal (95% CI)	**809**	**793**		**0.34 [0.18, 0.61]**
Total events: 13 (Any heparin + ASA), 39 (ASA)				
Heterogeneity: Chi^2 = 1.06, df = 1 (P = 0.30); I^2 =6%				
Test for overall effect: Z = 3.55 (P = 0.00039)				
2 UFH				
Doucet 2000	0/95	0/96		0.0 [0.0, 0.0]
Gurfinkel 1995	4/70	4/37		0.53 [0.14, 1.99]
Holdright 1994	42/154	40/131		0.89 [0.62, 1.29]
RISC 1990	12/210	14/189		0.77 [0.37, 1.63]
Theroux 1988	4/122	8/121		0.50 [0.15, 1.60]
Subtotal (95% CI)	**651**	**574**		**0.80 [0.58, 1.08]**
Total events: 62 (Any heparin + ASA), 66 (ASA)				
Heterogeneity: Chi^2 = 1.38, df = 3 (P = 0.71); I^2 =0.0%				
Test for overall effect: Z = 1.45 (P = 0.15)				
3 UFH + warfarin				
Cohen 1990	0/37	1/32		0.29 [0.01, 6.87]
Cohen 1994	4/105	9/109		0.46 [0.15, 1.45]
Subtotal (95% CI)	**142**	**141**		**0.43 [0.15, 1.28]**
Total events: 4 (Any heparin + ASA), 10 (ASA)				
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%				
Test for overall effect: Z = 1.52 (P = 0.13)				
Total (95% CI)	**1602**	**1508**		**0.61 [0.47, 0.80]**
Total events: 79 (Any heparin + ASA), 115 (ASA)				
Heterogeneity: Chi^2 = 9.52, df = 7 (P = 0.22); I^2 =26%				
Test for overall effect: Z = 3.62 (P = 0.00029)				

Analysis 6.1. Comparison 6 Incidence of major bleeds over all time periods, Outcome 1 Heparin + ASA vs ASA.

Review: Heparin versus placebo for acute coronary syndromes

Comparison: 6 Incidence of major bleeds over all time periods

Outcome: 1 Heparin + ASA vs ASA

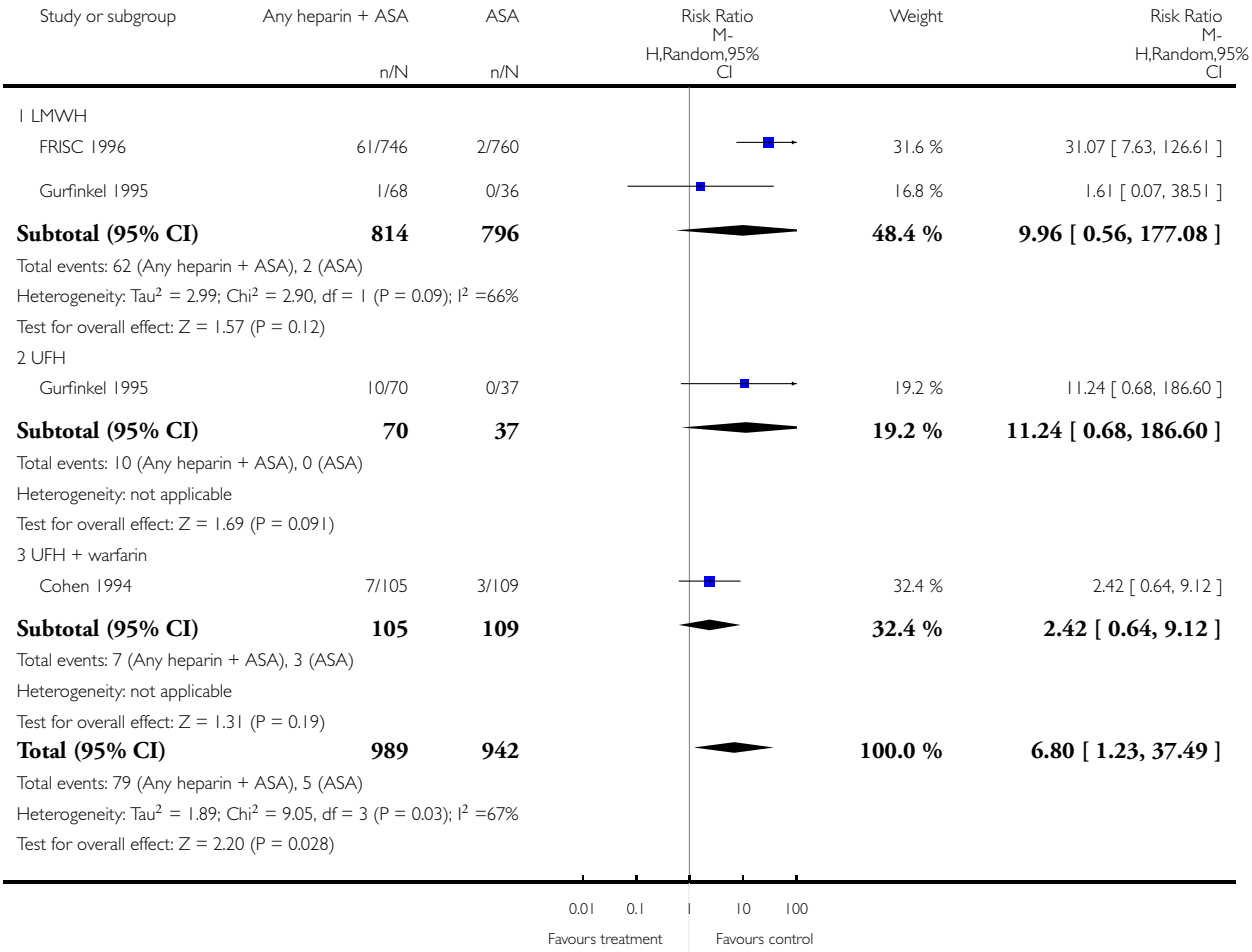


Analysis 7.1. Comparison 7 Incidence of minor bleeds over all time periods, Outcome 1 Heparin + ASA vs ASA.

Review: Heparin versus placebo for acute coronary syndromes

Comparison: 7 Incidence of minor bleeds over all time periods

Outcome: 1 Heparin + ASA vs ASA

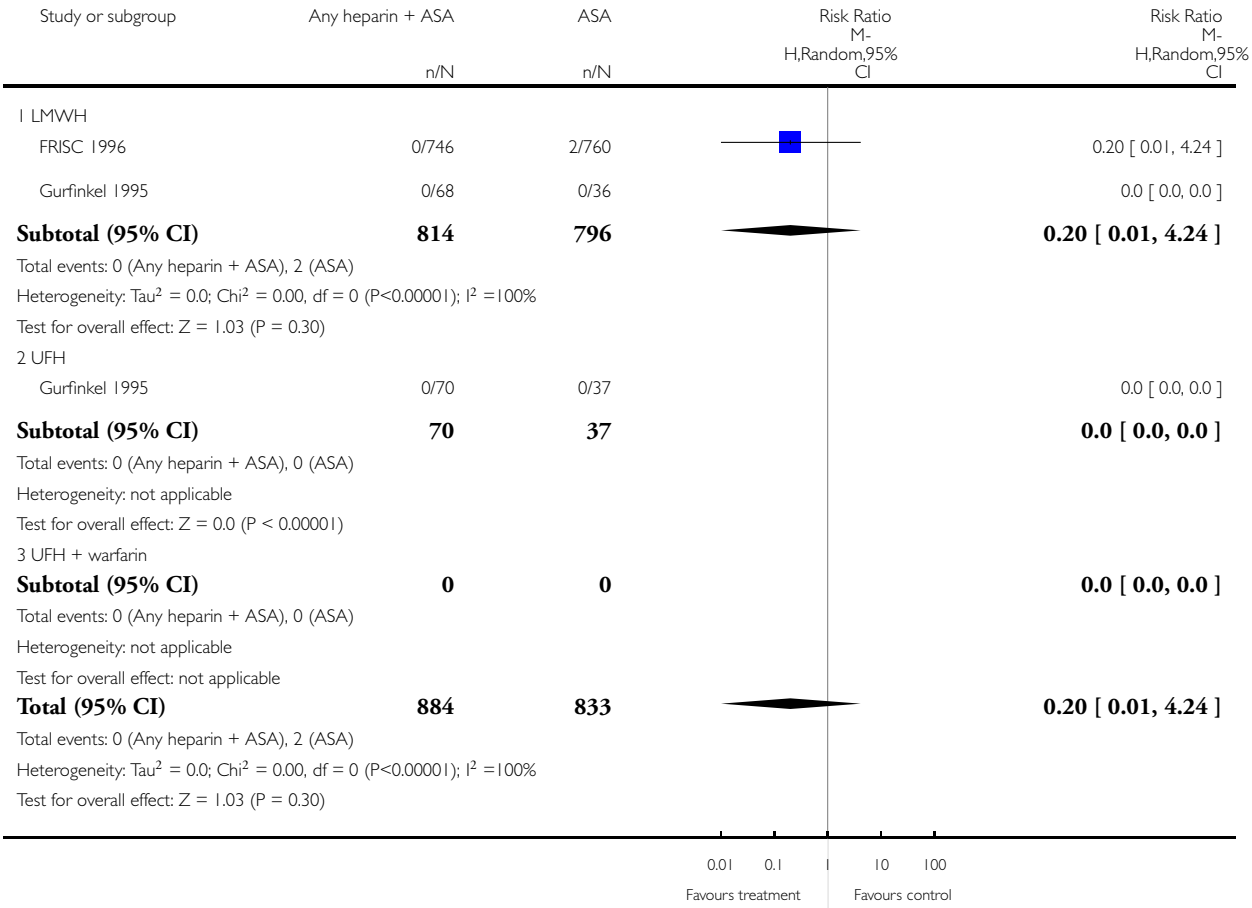


Analysis 8.1. Comparison 8 Incidence of thrombocytopenia over all time periods, Outcome 1 Heparin + ASA vs ASA.

Review: Heparin versus placebo for acute coronary syndromes

Comparison: 8 Incidence of thrombocytopenia over all time periods

Outcome: 1 Heparin + ASA vs ASA



FEEDBACK

From David Cundiff, 28 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 favored 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 favored 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 favored 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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Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. 10.1016/j.jacc.2007.02.013. *J Am Coll Cardiol.* August 14, 2007;50(7):e1-157.

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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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1. Magee K, Sevcik WW, Moher D, Rowe BH. Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD002132. DOI: 10.1002/14651858.CD002132.

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Contributors

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WHAT'S NEW

Last assessed as up-to-date: 27 January 2008.

Date	Event	Description
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

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 2, 2008

Date	Event	Description
8 September 2008	Amended	Converted to new review format.
28 January 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

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. Primary author.

Moher D: Protocol development, statistical methods support, and editing manuscript.

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

Campbell S: study selection and quality assessment.

DECLARATIONS OF INTEREST

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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