Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes (Review)

Magee K, Sevcik WW, Moher D, Rowe BH

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[Intervention Review]

Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Kirk Magee[1], William W Sevcik[2], David Moher[3], Brian H Rowe[4]

[1]Department of Emergency Medicine, Dalhousie University, Halifax, Canada. [2]Division of Emergency Medicine, Capital Health Authority, Edmonton, Canada. [3]Ottawa Hospital Research Institute, Ottawa, Canada. [4]Department of Emergency Medicine, University of Alberta, Edmonton, Canada

Contact address: Kirk Magee, Department of Emergency Medicine, Dalhousie University, Queen Elizabeth II Health Sciences Centre, Halifax Infirmary, 1796 Summer Street, Halifax, Nova Scotia, B3H 3A7, Canada. kmagee@dal.ca. kmagee@hfx.eastlink.ca.

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ABSTRACT

Background

Acute coronary syndromes (ACS) are an important source of morbidity and mortality. Despite weak evidence for the use of unfractionated heparin (UFH) for acute coronary syndromes it is considered an accepted treatment for unstable angina and non-ST segment elevation myocardial infarction (MI). However, evidence suggests low molecular weight heparins (LMWH) are safer and more effective than UFH in the treatment and prevention of other thrombotic disorders.

Objectives

To assess the effects of LMWH compared to UFH for acute coronary syndromes.

Search methods

We searched the Cochrane Controlled Trials Register (The Cochrane Library Issue 4, 2000), MEDLINE (January 1966 to December 2000), EMBASE (1980 to December 2000) and CINAHL (1982 to December 2000) and reference lists of articles. Authors of all include studies, and pharmaceutical industry representatives, were contacted to determine if unpublished studies, which met the inclusion criteria, were available.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 subcutaneous LMWH versus intravenous UFH in people with acute coronary syndromes (unstable angina or non-ST segment elevation MI).

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.

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Main results

We identified 27 potentially relevant studies, 7 studies (11,092 participants) were included in this review.

We found no evidence for difference in overall mortality between the groups treated with LMWH and UFH (RR = 1.0; 95% CI: 0.69, 1.44).

Some pooled outcomes showed some evidence of heterogeneity, few of the pooled outcomes were statistically heterogeneous most were homogeneous.

LMWH reduced the occurrence of MI (RR = 0.83; 95% CI: 0.70, 0.99) and the need for revascularization procedures (RR = 0.88; 95% CI: 0.82, 0.95). We found no evidence for difference in occurrence of recurrent angina (RR = 0.83; 95% CI: 0.68, 1.02), major bleeds (RR = 1.00; 95% CI: 0.80, 1.24) or minor bleeds (RR = 1.40; 95% CI: 0.66, 2.90). A decrease in the incidence of thrombocytopenia (RR = 0.64; 95% CI: 0.44, 0.94) was observed for patients given LMWH. From these results, 125 patients need to be treated with LMWH to prevent 1 additional MI and 50 patients need to be treated to prevent 1 revascularization procedure. Insufficient data exist to compare different types of LMWH.

Authors' conclusions

LMWH and UFH had similar risk of mortality, recurrent angina, and major or minor bleeding but LMWH had decreased risk of MI, revascularization and thrombocytopenia. New trials with longer follow up are required.

PLAIN LANGUAGE SUMMARY

Low molecular weight heparins reduce the number of heart attacks and cause fewer complications after an acute coronary syndrome compared to unfractionated heparin

Blood clots in the arteries leading to the heart can cause acute coronary syndrome: unstable angina (a feeling of tightness in the chest) or a type of heart attack. Drugs that dissolve clots (such as aspirin) or thin the blood (such as heparin) can relieve the problem. Unfractionated heparin (UFH) thins the blood, but can cause a serious but rare adverse effect. Low molecular weight heparin (LMWH) is a new type of heparin. The review of trials found that UFH and LMWH were equally effective in preventing death, but LMWH prevented more heart attacks and caused fewer complications.

BACKGROUND

Unstable angina is characterized by endovascular thrombus formation. It is thought that atherosclerotic plaque rupture or disruption results in activation of the coagulation and platelet systems with subsequent formation of a labile thrombus. This thrombus creates a temporary occlusion of the coronary arteries lasting from 10 to 20 minutes (Fuster 1995). This temporary reduction in blood flow to myocardial tissue leads to typical symptoms resulting in presentation to an acute care setting, such as hospital emergency departments. Most patients with this problem are admitted to hospital to avoid or detect a myocardial infarction (MI). Prior to the 1990s, a significant proportion of patients admitted with unstable angina progressed to myocardial infarction (MI) or died in hospital (Cairns 1989).

The diagnosis of unstable angina and non-ST segment elevation MI (also referred to as a non-Q wave MI) are common reasons for presentations to the emergency setting and are collectively referred to as acute coronary syndromes. Non-ST segment elevation myocardial infarction is differentiated from unstable angina by presence of elevated cardiac enzyme markers (creatine kinase or troponin) detected in the blood. Management of acute coronary syndromes is similar for both disorders and has advanced dramatically in the last decade. Current treatment includes aspirin, oxygen, bed rest and other therapeutic and procedural interventions. Despite weak evidence, the use of unfractionated heparin (UFH) in acute coronary syndromes is now considered an accepted treatment standard for non-ST segment elevation MI and unstable angina (Theroux 1988, RISC 1990). Unfortunately, there are many logistical problems (e.g. need for therapeutic monitoring, regular adjustments in treatment, etc.) and side effects (e.g. mi-

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nor and major bleeding) associated with its use. Even with aspirin treatment in combination with UFH combination therapy, there is still a 20% failure rate (death, MI or recurrent angina) at three months (Cohen 1998). As well, agreement on the diagnosis of unstable angina is not uniform. Consequently, many patients receive unnecessary and potentially harmful treatment while those who need this treatment may go untreated. Moreover, UFH demonstrates a variable dose-response anticoagulation effect, requiring repeated monitoring of patients' coagulation profiles. It is not uncommon for patients to be sub-therapeutic many hours after the initiation of treatment (Antman 1996). Finally, with UFH there is the significant risk of hemorrhagic complications and immune-mediated heparin-induced thrombocytopenia (HIT).

Low molecular weight heparins (LMWH) are newer agents produced by the depolymerization of standard UFH into smaller fragments (Fareed 1998). LMWH lack some of the shortcomings of UFH in that they have a fixed-dose anticoagulation effect, fewer bleeding complications, and a lower incidence of HIT (Warkentin 1995). Traditionally, LMWH have been considered to be equivalent to UFH in acute coronary syndrome and venous thromboembolism but cost has been cited as a reason for the continued use of UFH. However, recent systematic reviews have demonstrated that LMWH are safer and more efficacious in the treatment of venous thromboembolism (Lensing 1995, Siragusa 1996, Columbus 1997).

Currently, there is considerable interest in the use of LMWH in the treatment of acute coronary syndromes given its ease of use, cost efficiency, and more favorable therapeutic profile compared to UFH. Indeed, enoxaparin has already been approved in the United States for use in unstable angina and non-ST segment elevation MI. Despite numerous studies comparing LMWH to UFH, the various trials have been small, emphasize different outcomes and use various control group regimens for both LMWH and UFH, which makes comparisons difficult without a formal systematic review. Although there have been numerous reviews regarding the use of LMWH in acute coronary syndrome, they have, through their methodological limitations, lacked the power of a formal systematic review. This systematic review of LMWH in the acute treatment of acute coronary syndrome aims to fill that void. In view of the numerous clinical trials examining the role of LMWH in this field, we performed a focused, structured systematic review of LMWH versus UFH in the early treatment of acute coronary syndromes.

GLOSSARY

ACS
Acute coronary syndromes. A collection of symptoms indicating acute myocardial infarction or unstable angina.
AMI
Acute myocardial infarction "Heart Attack".
ASA
Acetyl salicylic acid "Aspirin".
CK
Creatine kinase, a serum enzyme found in the blood of a person from six hours to 72 hours after a myocardial infarction. Can be used to determine if someone has had a myocardial infarction. Can be found in the blood for other reasons.
ECG (Electrocardiogram)
A recording of the electrical activity of the heart on a moving strip of paper. The electrocardiogram detects and records the electrical potential of the heart during contraction.
LMWH
Low molecular weight heparin, a compound that thins the blood and helps prevent thrombus formation.
MI
Myocardial infarction "Heart Attack".
MB
Isoenzyme of creatine kinase, serum enzyme found in the blood of a person from six hours to 72 hours after a myocardial infarction. The MB isoenzyme is very specific to indicating heart muscle damage. Can be used to determine if someone has had a myocardial infarction.
PTCA
Percutaneous Transluminal Coronary Angioplasty, a minimally invasive technique for dilating blocked coronary arteries used both in acute and chronic myocardial ischemia.
Revascularization
Refers to the need to perform more surgery on the coronary arteries to prevent more damage to the heart.
UFH
Unfractionated Heparin, a compound that thins the blood and helps prevent thrombus formation.
Unstable angina
Angina that is new onset or prior existing angina which is increasing in severity, duration or frequency.

OBJECTIVES

To compare the effects (harms and benefits) of low molecular weight heparins (LMWH) with unfractionated heparins (UFH) for the treatment of patients with acute coronary syndromes with respect to death, myocardial infarction, recurrent angina and side effects.

METHODS

Criteria for considering studies for this review

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Types of studies

Randomized controlled trials that were blinded, and randomized controlled trials that were not blinded.

Types of participants

Only studies which included adult patients (> 18 years of age) presenting with acute coronary syndrome requiring treatment within 72 hours of presentation were eligible. For this review, we defined acute coronary syndrome to include unstable angina and non-ST segment elevation MI. Unstable angina was defined 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. Non-ST segment elevation MI was defined as chest pain without ST segment elevation and elevation of relative cardiac enzymes (CK-MB (MB isoenzyme of creatine kinase) greater than the upper normal limit, or total creatine kinase (CK) greater than twice the usual upper limit). Studies involving hospitalized patients, those with stable angina, volunteers, or those who presented outside of emergency department (emergency room, accident and emergency department) settings were excluded.

Types of interventions

All studies had to include patients randomized to receive treatment with either subcutaneous LMWH or intravenous UFH within 72 hours of presentation.

Types of outcome measures

All clinically relevant patient outcomes were considered. Outcomes included:

- death;
- MI;
- recurrent angina (anginal chest pain that requires nitroglycerin infusion to be restarted);
- revascularization procedures (e.g., angioplasty, stenting, bypass grafting, etc.);
- major hemorrhage (fall in hemoglobin level of >20 g/L; requirement for transfusion; intracranial, retroperitoneal, or intraocular bleeding; hemorrhage resulting in death or cessation of the study treatment);
- minor hemorrhage (any clinically important bleed that did not qualify as major, e.g. epistaxis, ecchymosis or hematoma, or macroscopic hematuria);
- thrombocytopenia (e.g. platelet count decrease during study period to <100 x 10-9/L);
- allergic reactions (e.g. rash, asthma, shock, etc.).

Three follow-up periods were considered for sub-groups: less than 48 hours (acute), 3 to 14 days (sub-acute), and greater than 14 days (late). However, all follow-up intervals were accepted.

Search methods for identification of studies

We searched the Cochrane Controlled Trials Register (The Cochrane Library Issue 4,2000), MEDLINE (January 1966 to December 2000), EMBASE (1980 to December 2000) and CINAHL (1982 to December 2000) and reference lists of articles. There were no language or publication restrictions and no publication status restrictions in this review.

The search consisted of the following terms:

a) heparin OR low molecular weight heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin

AND

b) angina OR angina pectoris.

Reference lists of all available primary studies and review articles were reviewed by one author (KM) to identify potentially relevant citations. Inquires 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 that manufacture LMWH were contacted for any unpublished or interim results on the use of LMWH on patients with acute coronary syndromes. Finally, personal contact with colleagues, collaborators and other trialists working in the field of acute coronary syndromes was made to identify other 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, BHR). From the potentially relevant articles, the same two reviewers independently selected trials (based on the full text format) for inclusion in this review. Agreement was measured using simple agreement and kappa (k) statistics. Disagreement was resolved by consensus or third party adjudication. Independent reviewers documented the content 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. Using the Cochrane approach to assessment of allocation concealment (Mulrow 1994), all trials were scored using the following principals:

Grade A: Adequate concealment;

Grade B: Uncertain;

Grade C: Clearly inadequate concealment.

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Inter-rater reliability was measured by using simple agreement, kappa, and weighted kappa statistics.
In addition, each study was assessed for validity using a 0-5 scale described by Jadad (Jadad 1996) and summarized as follows:
1) Was the study described as randomized (1=yes;0=no)?
2) Was the study described as double-blind (1=yes;0=no)?
3) Was there a description of withdrawals and dropouts (1=yes;0=no)?
4) Was the method of randomisation well described and appropriate (1=yes;0=no)?
5) Was the method of double blinding well described and appropriate (1=yes;0=no)?
6) Deduct 1 point if methods for randomization or blinding were inappropriate.
Inter-rater reliability was measured by using simple agreement, kappa, and weighted kappa statistics.

Data extraction

Data for the trials was extracted independently by two reviewers (BHR, KM) and entered into the Review Manager software program (Version 4.1).

Statistical considerations

An intention-to-treat analysis was used. Data from all trials were combined using the Meta analysis software in Review Manager. For dichotomous variables, individual and pooled statistics were calculated as relative risks (RR) with 95% confidence intervals (95% CI); a random effects (RE) model was used when more than 5 trials were pooled. When fewer trials or no heterogeneity was identified, a fixed effects (FE) 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.
Specific subgroups were planned a priori. First, to compare unstable angina to non-ST segment elevation MI and second, to compare results based on the specific LMWH used. Other planned sensitivity analyses were: mixed vs. random effects and methodological quality (high versus low). If significant heterogeneity ($p < 0.1$) existed, the groups were to be divided on the following order:
a) Methodological quality: using a "quality weighted" analysis to allow for use of all the trials.
b) Population: unstable angina versus unstable angina and non-ST segment elevation MI;
c) Intervention: different types of LMWH.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
The evidence for the use of LMWH in acute coronary syndrome is recent, appearing in the published literature within the last 5 years. With the exception of 3 smaller trials, most of the evidence is from 4 large multicentre trials representing 95% of the total number of subjects studied.
Designs: All studies were RCTs; however, not all were double blind.
Populations: Traditionally, heparin was often started in the treatment of acute coronary syndromes based on history alone. In these studies, patients were selected for inclusion on the basis of a more narrow definition. They had to have a history of angina plus one of the following: a previous history of known coronary artery disease, ECG changes, or cardiac enzyme elevation.
Interventions: The studies included 11,092 patients and involved four different LMWH. In total, 7045 patients (63%) were eligible to receive enoxaparin, 2535 patients (23%) nadroparin, 1482 patients (13%) dalteparin and 40 patients (<1%) tinzaparin. Most patients received the intervention within 24 hours of the onset of symptoms; however, some patients received it as late as 48 hours in one trial (FRAXIS 1999) and 72 hours in another (FRIC 1997). The duration of therapy varied among the studies with the majority of patients receiving treatment for 5 to 8 days. Aspirin (75 to 325 mg per day) was a standard concommitant 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, MI, recurrent angina, revascularization and major bleeds were the most commonly reported outcomes across the studies. Death was reported as "all-cause" and secondary to MI in most studies. Myocardial infarction was defined by either the appearance of new significant ECG changes or by the elevation of cardiac enzymes in association with chest pain. The definition of recurrent angina varied among the studies; however, most required a history of typical chest pain accompanied by ECG changes. Several studies (ESSENCE 1997, FRIC 1997, TIMI 11B 1999) defined recurrent angina as any new angina requiring readmission to hospital and the institution of nitroglycerin or heparin infusions or recurrent symptoms prompting a decision to perform a revascularization procedure. 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 4 studies each.
The timing of the end points was inconsistent among the trials ranging from 48 hours to 3 months. Most endpoints were recorded over a 5 to 8 day period. We have divided the timing of the outcomes into clinically relevant time periods: early (<48 hours), subacute (3-14 days), and late (greater than 14 days).

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Risk of bias in included studies

Overall there was a dichotomy in the methodological quality of the studies. The larger multicentre studies tended to be rated as high quality. They were double-blind, placebo controlled, demonstrated an appreciation of the need for concealment of allocation, and reported a sufficient number of clinically relevant outcomes. The smaller studies tended to be of lower quality.

Using the Jadad method, 3 studies representing 84% of enrolled subjects were rated as "strong" (ESSENCE 1997, FRAXIS 1999, TIMI 11B 1999) and 4 were rated as "weak" (Gurfinkel 1995, Suvarna 1997, FRIC 1997, Godoy 1998). The median score was 2 with an interquartile range of 2 to 4. Using the Cochrane methodology, 5 of the 7 studies had unclear concealment of allocation.

Effects of interventions

The computerized search of EMBASE, MEDLINE and CINAHL identified over 200 original publications. Independent review of the abstracts and titles of these publications identified 23 potentially relevant studies. The kappa statistic for inter-rater agreement on including or excluding potential trials was 0.63. Additional references were added from bibliographic searching of relevant articles and overviews (2), from correspondence with authors (1) and from an updated search (1). In total, 27 studies were reviewed for inclusion in this systematic review. Independent review of these potentially relevant articles resulted in 7 included studies (6 in English and 1 in a foreign language), with a total of 11,092 patients being included in this systematic review. Two potentially relevant abstracts were not included as detailed methodologies and outcomes could not be obtained (Correia 1996, Bednarkiewicz 1997). One recently published study (ASSENT 3) is still awaiting assessment. The full list of excluded studies and reasons for exclusion are listed in the Excluded Studies section.

Outcomes will be discussed in the main domains as follows. Early, up to 48 hours after starting treatment (n=7081); sub acute, 3 to 14 days after starting treatment (n=11128) and late, 30 days or more after starting treatment (n=5488).

Death

Overall LMWH did not appear to reduce the incidence of death compared to UFH for any of the time periods. The pooled data for all time periods for LMWH versus UFH (11092 participants) showed some evidence of heterogeneity (p = 0.08) and a random effects model was used when pooling the data. When data from all three time periods were pooled we found the risk of death to be similar in both groups, LMWH and UFH (RR = 1.00; 95% CI: 0.69, 1.44).

Myocardial infarction

LMWH were superior to UFH in preventing MI (RR = 0.83; 95% CI: 0.70, 0.99) when data were pooled from all time periods following onset of treatment (n=11092). There was no heterogeneity in this pooled analysis (p = 0.39) of data from 7 trials. LMWH were superior to UFH in preventing MI (RR = 0.83; 95% CI: 0.69, 0.99) at 3 to 14 days following onset of treatment (n= 11128). There was no heterogeneity in this pooled analysis (p = 0.26). We could find no evidence of a difference between LMWH and UFH for preventing MI at the early phase, up to 48 hours after starting treatment (n= 7081) or at the late phase 30 days or more after starting treatment (n=5488).

The overall incidence of MI was 4.2% (233/5580) for patients treated with LMWH, and 5.0% (276/5512) for those treated with UFH. Given the risk difference of 0.008, 125 patients would require treatment with LMWH to prevent one additional MI.

Recurrent angina

Recurrent angina was reported as an outcome in the early phase following treatment (n=3171), sub-acute phase 3 to 14 days following treatment (n=7218) and late phase, 30 days or more following treatment (n=5488). Over all time periods there was some evidence of heterogeneity (p = 0.07) and a random effects model was used to pool data. LMWH tended to reduce episodes of recurrent angina compared to UFH (RR = 0.83; 95% CI: 0.68, 1.02). For the most commonly reported outcome period (sub-acute), LMWH showed a trend towards preventing more episodes of recurrent angina than UFH, but this did not reach statistical significance using the random effect model (RR = 0.81; 95% CI: 0.65, 1.00). Heterogeneity was demonstrated (p = 0.08). The early and late periods in the two studies that reported these endpoints showed similar trends (ESSENCE 1997, FRAXIS 1999).

Revascularization procedures

Seven trials reported revascularization procedures within 2 weeks of admission to hospital (n=11128). Patients treated with LMWH experienced significantly fewer revascularization procedures compared to those who received UFH (RR = 0.88; 95% CI: 0.82, 0.95). No significant heterogeneity was identified in this result (p = 0.27). For the LMWH group, 14.2% (516/3642) experienced revascularization procedures compared to 16.1% (576/3576) in the UFH group. Given the risk difference of 0.02, 50 patients would need to be treated with LMWH to prevent one additional revascularization procedure.

Multiple end points

A combined multiple end point was recorded in the trials, it consisted of the numbers of deaths, MI, recurrent angina or revascularizations.

LMWH was superior to UFH (RR = 0.80; 95% CI: 0.67, 0.95) for the prevention of combined endpoints during the early phase,

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up to 48 hours after treatment (n=7081). LMWH was superior to UFH (RR = 0.80; 95% CI: 0.66, 0.98) for the prevention of combined endpoints during the sub-acute period, 3-14 days after treatment (n= 11128). Data from this analysis indicated heterogeneity ($p < 0.01$) and a random effects model was used to pool data from these trials. The data from these pooled studies describes three different LMWH: dalteparin, enoxaparin and nadroparin. Individually, only enoxaparin appeared better than UFH (fixed effects model RR = 0.85; 95% CI: 0.76, 0.94); no significant heterogeneity was identified in this result ($p = 0.86$). We found no evidence for difference between LMWH and UFH (RR = 0.90; 95% CI: 0.80, 1.01) at 30 days or more after starting treatment. The incidence of multiple end points in the group treated with LMWH was 12.5% (685/5492) compared to 14.1% (765/5422) in the group treated with UFH. Given the risk difference of 0.02, the number needed to treat with LMWH is 50 to prevent one event.

Side effects

We found no evidence that the incidence of major bleeds was different in those treated with LMWH and those treated with UFH (RR = 1.00; 95% CI: 0.80, 1.24).

Five trials, representing 78% of the total number of subjects studied, reported minor bleeds. There was significant heterogeneity in this estimate ($p < 0.00015$) and therefore, the random-effects model was used. Patients receiving LMWH demonstrated a higher occurrence of minor bleeds compared to those treated with UFH, but this effect was not statistically significant (RR = 1.40; 95% CI: 0.68, 2.90). Thrombocytopenia was a relatively rare event in the four trials that reported this outcome, occurring in only 1.5% of patients. However, significantly less thrombocytopenia was observed in patients receiving LMWH than UFH (RR = 0.64; 95% CI: 0.44, 0.94); there was no heterogeneity in this result ($p = 0.71$). In the LMWH group, 1.0% of patients developed thrombocytopenia compared to 1.8% in the UFH group. This represents a risk difference of 0.008. As such, 125 patients would have to be treated with LMWH to prevent one additional case of thrombocytopenia.

Sensitivity/Subgroup analyses

Sensitivity analyses based on a RE versus FE model yielded very similar results except where indicated. The point estimates remained essentially unchanged. Using a RE model, only differences in the revascularization rate and the incidence of thrombocytopenia reached a statistically significant level. Given the total number of patients included in our analyses, we feel that it is unlikely that we have missed any major papers that would significantly alter our pooled estimates and are thus justified in reporting results based on fixed effect modelling in cases where no heterogeneity exists. The trial quality assessment eliminated 4 papers (Gurfinkel 1995, Suvarna 1997, FRIC 1997, Godoy 1998); following this the outcomes were unchanged.

Subgroup analyses based on whether patients had unstable angina versus a non-ST segment elevation MI were not possible in this review, since subgroup data could not be obtained from the studies. Subgroup comparisons based on the different LMWH used were difficult to make due to small study numbers. It is interesting to note, however, that enoxaparin was the only individual subgroup to show a statistically significant benefit over UFH in any of the outcomes studied.

DISCUSSION

This systematic review examined the best available evidence for the use of LMWH in the emergency management of acute coronary syndromes. Several important points arise from this systematic review. The pooled results failed to demonstrate statistically significant evidence of a beneficial effect of LMWH in terms of mortality however a beneficial effect as great as a 30% reduction or a 44% increase in risk of death cannot be excluded. However, the LMWH treatment appeared to reduce the incidence of MI and the need for revascularization procedures. While these differences were indeed statistically significant, the absolute risk differences were small calling into question the clinical significance of the observed benefit of LMWH over UFH. Although the review failed to demonstrate bleeding differences between the treatments, using LMWH resulted in significantly less thrombocytopenia.

Overall, little heterogeneity was identified 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 seen included the incidence of recurrent angina, multiple endpoints and minor bleeds. This can in part be accounted for by subtle differences in study design: inclusion criteria, dosing regime and LMWH used. To a larger extent however, this heterogeneity may reflect the particular outcomes in question, the definitions of which varied between studies.

This systematic review illustrates the potential benefit of using LMWH in the early of treatment of acute coronary syndromes. Patients presenting with unstable angina or non ST segment elevation MI should be considered for a 5 to 8 day course of LMWH therapy in addition to ASA and standard anti-anginal therapy when they meet the criteria outlined in these studies. All 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 UFH for acute coronary syndrome. Therefore, we cannot recommend the indiscriminate substitution of LMWH for UFH. LMWH must be reserved for those patients with either non ST segment elevation MI or high-risk unstable

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angina as defined above. Furthermore, in those centres with active primary cardiac catheterization facilities, intravenous UFH represents a safer option than LMWH, as it has a much shorter half-life and is more easily reversed.

The difference between LMWH and UFH was most pronounced in reducing the "softer" outcome "revascularization procedure". There was some variation in the definition of this outcome among the various studies; however, LMWH also proved to be more efficacious in the prevention of MI compared to UFH such that 125 patients would need to be treated with LMWH to prevent one additional MI. This is similar to the difference between tPA and streptokinase commonly quoted in the MI literature (GUSTO 1993).

In terms of safety, LMWH appears to be superior to UFH. While previous systematic reviews demonstrated less major bleeding when LMWH was compared to UFH in venous thromboembolism we were unable to demonstrate differences between the treatments in major or minor bleeding. However, in both cases heterogeneity was present. Indeed, in keeping with previous studies, there was a lower incidence of thrombocytopenia, a rare but potentially life-threatening complication of heparinization.

This systematic review contrasts with previous systematic reviews in both scope and conclusions. While some have argued that it is an oversimplification to conduct meta-analyses of clinical trials that use different LMWH (Antman 1999), Sackett et al state that "a class effect is considered to be present when drugs with similar mechanisms of action generate relative risk reductions that are similar in direction and magnitude" (Sackett 1999). Previous reviews have demonstrated a class effect among the different preparations of LMWH in the treatment of venous thromboembolic disease. It would therefore seem logical to extend this argument to the use of LMWH in the treatment of acute coronary syndromes. A more recent systematic review (Eikelboom 2000) concluded "there is no convincing difference in efficacy or safety between LMWH and UFH." The Eikelboom systematic review did not include two trials (Gurfinkel 1995, Suvarna 1997) included in this study. Yet, their review still included the large bulk of patients (nearly 11,000 of the 11,092), so it is unlikely that this accounts for the difference in conclusions. As many of the point estimates were similar and only the 95% confidence intervals different, it may be that the difference in interpretation is based on fixed versus random effects modelling.

There is a possibility of publication bias in this systematic review. For example, by missing unpublished negative trials we may be over-estimating the effect of LMWH 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. There is also a possibility of study selection bias. 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.

These results are concordant with the most current recommendations made by the American Heart Association (Braunwald 2000, ACLS 2000). The AHA suggests using either LMWH or UFH for patients with intermediate to high risk unstable angina or non-ST segment elevation MI. Although LMWH appeared to be statistically superior to UFH, there was a relatively small reduction in absolute risk. The American Heart Association recommends using both heparin and IIb/IIIa glycoprotein inhibitors for high-risk patients. As the safety of combining LMWH and IIb/IIIa glycoprotein inhibitors has not yet been established the use of LMWH in this situation awaits further investigation.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review of randomized controlled trials supports the use of subcutaneous LMWH in the early treatment of acute coronary syndrome. Given to patients with a history of typical angina accompanied by either a past medical history of coronary artery disease or ECG/cardiac enzyme changes, LMWH was more efficacious in reducing MI and revascularization, but not mortality, with fewer serious side-effects than UFH. In this review, LMWH was 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 5 to 8 days. The small number of studies make it impossible to recommend a particular dosing regimen. Although it was impossible to compare the different preparations of LMWH directly, enoxaparin was the only LMWH which showed individual benefit over UFH.

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. Of the 4 large multi-centre studies, those using enoxaparin initiated treatment within 24 hours of the onset of symptoms compared to 48 and 72 hours for nadroparin and dalteparin, respectively. It would be interesting to determine whether the administration of LMWH would improve outcomes if administered in the Emergency Department, very early during the course of the hospital admission.

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- Given the subtle variations in treatment protocols, head to head comparisons of the various LMWH would be helpful in determining maximum efficacy.

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

- It is disappointing that a comprehensive range of outcomes and side effects over longer duration have not been reported. Trialists should aim to follow patients up for at least one month and report all causes of mortality, cardiovascular mortality, non-fatal MI, recent angina and revascularization rates.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

ESSENCE 1997

Methods	Design: Prospective, randomized, double-blind, parallel-group, multicenter trial Randomisation: not described. Blinding: double dummy trial, dummy heparin results, similar appearance of drug. Number excluded: not reported. Withdrawals: 367 (11.6%) all well documented and evenly balanced. Baseline characteristics: no imbalance demonstrated; adjusted analyses performed
Participants	Location: 176 hospitals in 10 countries (North America, South America and Europe). Participants: 3171 patients 18 years of age or older. Unstable angina: Recent onset of angina at rest lasting at least 10 minutes and occurring within 24h before randomization. In addition, had to have one of the following three: ECG changes, previous MI or revascularization procedure, or invasive/noninvasive testing suggestive of ischemic heart disease. Non-Q wave MI: not included Exclusion criteria: left bundle branch block, pacemaker, persistent ST segment elevation, angina with established precipitating cause, contra-indications to anticoagulation, creatinine clearance < 30 ml/min
Interventions	Intervention: ASA 100-325 mg/d, enoxaparin 100 anti-factor Xa units/kg sc bid, placebo bolus and infusion. Control: ASA 100-325 mg/d, UFH 5000 IU iv then drip to keep PTT between 55-85 seconds. Timing: Trial therapy was administered for a minimum of 48h to a maximum of 8 days. Co-interventions: not permitted; patients excluded if treating MD deviated from protocol. Other co-interventions (e.g., oxygen, beta-blockers, nitroglycerine, etc) not well described
Outcomes	Acute Coronary Events: Recurrent angina, MI, death all reported. Urgent revascularization: reported End Point Definition: Triple end point for all cardiovascular events (angina, MI, death). Complication: Major bleeding, minor bleeding, and thrombocytopenia. Timing of assessment: Outcomes at 48h, 14 days, and 30 days.
Notes	Enoxaparin. We used the outcomes reported at 14 days for the pooled results. Correspondence with Pharmaceutical Company

Risk of bias

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

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FRAXIS 1999

Methods	Prospective, randomized, double-blind, parallel-group, multicenter trial
Participants	Patients 18 years of age or older with non-Q-wave MI or recent onset of rest angina lasting longer than 5 minutes or severe exertional angina and occurring within 48h before randomization. In addition, had to have ECG signs compatible with the clinical diagnosis or in cases of preexisting and documented LBBB, known CAD. If Q waves were present, a previous ECG tracing must confirm the long standing diagnosis
Interventions	Group I: ASA 325 mg/d, UFH 5000 IU iv then infusion titrated to PTT x 6 days. Group II: ASA 325 mg/d, nadroparin iv 86 AXa IU/kg then sc 86 AXa IU/kg bid x 6 days. Group III: ASA 325 mg/d, nadroparin iv 86 AXa IU/kg then sc 86 AXa IU/kg bid x 14 days
Outcomes	Outcomes at 6 days, 14 days, and 3 months. Cardiac death, AMI, refractory angina, recurrence of unstable angina, emergency revascularization, major hemorrhage, severe thrombocytopenia and other serious adverse events
Notes	Nadroparin. Includes non-Q-wave MI.

Risk of bias

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

FRIC 1997

Methods	Prospective, randomized, multinational parallel group design. In the acute phase, patients received open treatment with either LMWH or UFH for ~6 days. In the prolonged treatment phase between 6 and 45 days, patients received double blind treatment with LMWH or placebo
Participants	Consecutive patients with unstable angina or non-Q-wave MI were entered into the study within 72 hours of the last onset of chest pain. They had to satisfy a modified Braunwald classification for unstable coronary artery disease as well as have ECG changes
Interventions	Therapy for a total of ~6 days. Goup I: ASA 75-165 mg/d, dalteparin 120IU/kg sq bid. Group II: ASA 75-165 mg/d, UFH 5000 IU iv then 1000 IU/h titrated to PTT (1.5 x normal); after 48h, clinician had choice of continuing with UFH infussion or switching to UFH 12 500 IU sc bid. Other antianginal medications at the discretion of the clinician
Outcomes	Outcomes over 6 days. Death, AMI, recurrent angina, urgent revascularization, major and minor hemmorrhage, thrombocytopenia, and allergic reaction
Notes	Dalteparin. Includes non-Q-wave MI. Data only used from the acute phase of the study

Risk of bias

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

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Godoy 1998

Methods	Prospective, randomized, multicenter trial.
Participants	Patients with a history of angina at rest lasting longer than 15 minutes occurring within 24h previous to admission. In addition, had to have one of the following: ECG changes, documented history of CAD, or elevated CPK
Interventions	Therapy administered for 3 to 5 days. Group I: ASA 200 mg, NTG iv, UFH 5000 IU iv then 800 IU/h titrated to PTT (2-2.5 x control). Group II: ASA 200 mg, NTG iv, UFH 5000 IU iv then nadroparin 0. 6 ml sc q12h. Patient also received beta-blockers, calcium-blockers and oral nitrates to maintain HR-60 and SBP<130 mmHg
Outcomes	Over 3 to 5 days. Recurrent angina (2 or more episodes of angina associated with ECG changes and required adjustment of medical treatment or urgent angiographic study within 4 to 72h of initiating anticoagulation treatment), AMI, and urgent revascularization
Notes	Nadroparin. Included non-Q-wave MI. Randomization done in an open form

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Gurfinkel 1995

Methods	Prospective, randomized, single-blind trial.
Participants	Patients 21 years of age or older with unstable angina defined as recent onset or prolonged (> 10 min) spontaneous rest pain occurring within 24 h of randomization. As well, had to have evidence of underlying ischemic heart disease as shown by at least one of the following: ECG changes, previous MI or CABG, history of typical exertional angina, angiography with 70% lumenal narrowing, angina at rest with ECG changes diagnosed by two cardiologists, positive stress test
Interventions	Therapy continued for 5 to 7 days. Group I: ASA 200 mg/d. Group II: ASA 200 mg/d, UFH 5000 IU iv then 400 IU/kg/d titrated to PTT (2 x normal). Group III: ASA 200 mg/d, CY 216 nadroparin calcium 214 IUC/kg anti-Xa sc bid, heparin placebo. Treatment with standard antianginal therapy
Outcomes	Over 5 to 7 days. Death, MI, recurrent angina, urgent revascularization, silent ischemia, major/minor hemorrhage, and thrombocytopenia
Notes	Nadroparin. Only data from groups II and III used.

Risk of bias

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

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Suvarna 1997

Methods	Randomization was not blinded. Patients were assigned alternately to one of the two groups on admission
Participants	Patients more than 21 years of age who presented with symptoms of unstable angina occurring within 24 hours of randomization. Associated evidence of CAD was required (ECG changes, previous MI, presence of at least 70% luminal narrowing on prior angiogram, past positive stress test)
Interventions	Therapy for 5 days. Group I: Tinzaparin 3500 units sc bid, ASA 160 mg/d, IV nitro glycerin. Group II: UFH 5000 IU iv then 1000 IU/hr titrated vs. PTT (about twice normal), ASA 160 mg/d, IV nitro glycerin
Outcomes	Over 5 days. Angina, AMI, urgent revascularization, major hemorrhage, minor hemorrhage
Notes	Tinzaparin.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

TIMI 11B 1999

Methods	Prospective, randomized, double-blind, double-dummy, multi-center trial
Participants	Patients with non-Q-wave MI or unstable angina lasting more than 5 minutes and occurring within 24h of study enrolment. Additionally, patients must have ECG changes or an elevated serum cardiac marker to be eligible for enrolment
Interventions	Therapy for ~8 days. Group I: ASA 100-325 mg/d, enoxaparin 30 mg iv then 1 mg/kg sc q12h x 8 days or until discharge. UFH placebo. Group II: ASA 100-325 mg/d, UFH 70 IU/kg iv bolus then 15 IU/kg/hr titrated to PTT (1.5-2.5 x control) x 8 days or until discharge. LMWH placebo. Beta-blockers, nitrates, other anti-platelets and calcium blockers per discretion of the treating physician
Outcomes	Outcomes over 8 days. Death, MI, urgent revascularization.
Notes	Enoxaparin. Includes non-Q-wave MI. Data only used from the in-hospital acute phase of the study

Risk of bias

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

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

Study	Reason for exclusion
Ahrens 1998	Study was not a randomised controlled trial.
Andersen 1998	LMWH Vs UFH was not the primary research question.
Bednarkiewicz 1997	Abstract. Insufficient data.
Correia 1995	Unable to separate patients with ACS from those with AMI or those who underwent PCTA
Correia 1996	Abstract. Insufficient data
Fox 1998	Study was not a randomised controlled trial.
FRISC 1996	LMWH was only compared versus placebo
Kirichenko 1994	Did not report clinically relevant outcomes
REDUCE 1998	Patients were inpatients undergoing PTCA.
Talley 1997	Study was not a randomised controlled trial.
TIMI 11A 1997	Patients were not randomized and LMWH was not compared versus UFH. This was a dose ranging study
TRIM 1997	LMWH was not the primary research question.

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DATA AND ANALYSES

Comparison 1. LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of early death (48 hours)	2	7081	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.71, 2.92]
1.1 Enoxaparin vs unfractionated heparin	2	7081	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.71, 2.92]
2 Incidence of death in sub-acute phase (3-14 days)	7	11128	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.79, 1.36]
2.1 Enoxaparin vs unfractionated heparin	2	7081	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.24]
2.2 Dalteparin vs unfractionated heparin	1	1482	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [1.00, 12.74]
2.3 Nadroparin vs unfractionated heparin	3	2525	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.65, 2.18]
2.4 Tinzaparin vs unfractionated heparin	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Incidence of late deaths (> or = 30 days)	2	5488	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.73, 1.27]
3.1 Enoxaparin vs unfractionated heparin	1	3171	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.55, 1.17]
3.2 Nadroparin vs unfractionated heparin	1	2317	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.79, 1.77]
4 Incidence of death over all periods	7	11092	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.69, 1.44]
4.1 Enoxaparin vs unfractionated heparin	2	7045	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.61, 1.05]
4.2 Dalteparin vs unfractionated heparin	1	1482	Risk Ratio (M-H, Random, 95% CI)	3.57 [1.00, 12.74]
4.3 Nadroparin vs unfractionated heparin	3	2525	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.79, 1.77]
4.4 Tinzaparin vs unfractionated heparin	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5 Incidence of early MI (< 48 hours)	2	7081	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.47, 1.07]
5.1 Enoxaparin vs unfractionated heparin	2	7081	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.47, 1.07]
6 Incidence of MI in sub-acute period (3-14 days)	7	11128	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.96]
6.1 Dalteparin vs unfractionated heparin	1	1482	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.44, 1.46]
6.2 Enoxaparin vs unfractionated heparin	2	7081	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.56, 0.90]
6.3 Nadroparin vs unfractionated heparin	3	2525	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.75, 1.61]

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6.4 Tinzaparin vs unfractionated heparin	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Incidence of late MI (> or = 30 days)	2	5488	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.71, 1.13]
7.1 Enoxaparin vs unfractionated heparin	1	3171	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.54, 1.03]
7.2 Nadroparin vs unfractionated heparin	1	2317	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.79, 1.52]
8 Incidence of MI over all periods	7	11092	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.70, 0.99]
8.1 Enoxaparin vs unfractionated heparin	2	7045	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.62, 0.95]
8.2 Dalteparin vs unfractionated heparin	1	1482	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.44, 1.46]
8.3 Nadroparin vs unfractionated heparin	3	2525	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.74, 1.41]
8.4 Tinzaparin vs unfractionated heparin	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Incidence of early recurrent angina (48 hours)	1	3171	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.08]
9.1 Enoxaparin vs unfractionated heparin	1	3171	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.08]
10 Incidence of recurrent angina in subacute period (3-14 days)	6	7218	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.65, 1.00]
10.1 Dalteparin vs unfractionated heparin	1	1482	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.74, 1.70]
10.2 Enoxaparin vs unfractionated heparin	1	3171	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
10.3 Nadroparin vs unfractionated heparin	3	2525	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.37, 1.09]
10.4 Tinzaparin vs unfractionated heparin	1	40	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.22, 2.01]
11 Incidence of late angina (> or = 30 days)	2	5488	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.81, 1.02]
11.1 Enoxaparin vs unfractionated heparin	1	3171	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.75, 1.02]
11.2 Nadroparin vs unfractionated heparin	1	2317	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.80, 1.15]
12 Incidence of recurrent angina over all periods	6	7218	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.68, 1.02]
12.1 Enoxaparin vs unfractionated heparin	1	3171	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.75, 1.02]
12.2 Dalteparin vs unfractionated heparin	1	1482	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.74, 1.70]
12.3 Nadroparin vs unfractionated heparin	3	2525	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.37, 1.13]
12.4 Tinzaparin vs unfractionated heparin	1	40	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.22, 2.01]
13 Revascularization	7	11128	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.82, 0.95]
13.1 Dalteparin vs unfractionated heparin	1	1482	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.58, 1.40]

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13.2 Enoxaparin vs unfractionated heparin	2	7081	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.77, 0.93]
13.3 Nadroparin vs unfractionated heparin	3	2525	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.08]
13.4 Tinzaparin vs unfractionated heparin	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.94]
14 Multiple end point (< 48 hours)	2	7081	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.67, 0.95]
14.1 Enoxaparin vs unfractionated heparin	2	7081	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.67, 0.95]
15 Multiple end point events (3-14 days)	7	11128	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.66, 0.98]
15.1 Dalteparin vs unfractionated heparin	1	1482	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.87, 1.71]
15.2 Enoxaparin vs unfractionated heparin	2	7081	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.76, 0.94]
15.3 Nadroparin vs unfractionated heparin	3	2525	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.33, 1.15]
15.4 Tinzaparin vs unfractionated heparin	1	40	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.23, 1.37]
16 Multiple end point events (> or = 30 days)	2	5488	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.80, 1.01]
16.1 Enoxaparin vs unfractionated heparin	1	3171	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.74, 0.97]
16.2 Nadroparin vs unfractionated heparin	1	2317	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.83, 1.44]
17 Major bleeds	6	11022	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.80, 1.24]
18 Minor bleeds	5	8705	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.68, 2.90]
19 Thrombocytopenia	4	7608	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.44, 0.94]

Analysis 1.1. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 1 Incidence of early death (48 hours).

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 1 Incidence of early death (48 hours)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Enoxaparin vs unfractionated heparin					
ESSENCE 1997	8/1607	7/1564		54.2 %	1.11 [0.40, 3.06]
TIMI 11B 1999	11/1953	6/1957		45.8 %	1.84 [0.68, 4.96]
Total (95% CI)	**3560**	**3521**		**100.0 %**	**1.44 [0.71, 2.92]**
Total events: 19 (Treatment), 13 (Control)					
Heterogeneity: Chi^2 = 0.48, df = 1 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 1.02 (P = 0.31)					

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Analysis 1.2. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 2 Incidence of death in sub-acute phase (3-14 days).

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 2 Incidence of death in sub-acute phase (3-14 days)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Enoxaparin vs unfractionated heparin				
ESSENCE 1997	36/1607	36/1564		0.97 [0.62, 1.54]
TIMI 11B 1999	34/1953	41/1957		0.83 [0.53, 1.30]
Subtotal (95% CI)	**3560**	**3521**		**0.90 [0.65, 1.24]**
Total events: 70 (Treatment), 77 (Control)				
Heterogeneity: Chi^2 = 0.23, df = 1 (P = 0.63); I^2 =0.0%				
Test for overall effect: Z = 0.66 (P = 0.51)				
2 Dalteparin vs unfractionated heparin				
FRIC 1997	11/751	3/731		3.57 [1.00, 12.74]
Subtotal (95% CI)	**751**	**731**		**3.57 [1.00, 12.74]**
Total events: 11 (Treatment), 3 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.96 (P = 0.050)				
3 Nadroparin vs unfractionated heparin				
FRAXIS 1999	23/1166	19/1151		1.19 [0.65, 2.18]
Godoy 1998	0/30	0/40		0.0 [0.0, 0.0]
Gurfinkel 1995	0/68	0/70		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1264**	**1261**		**1.19 [0.65, 2.18]**
Total events: 23 (Treatment), 19 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.58 (P = 0.56)				
4 Tinzaparin vs unfractionated heparin				
Suvarna 1997	0/20	0/20		0.0 [0.0, 0.0]
Subtotal (95% CI)	**20**	**20**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Total (95% CI)	**5595**	**5533**		**1.04 [0.79, 1.36]**
Total events: 104 (Treatment), 99 (Control)				
Heterogeneity: Chi^2 = 4.84, df = 3 (P = 0.18); I^2 =38%				
Test for overall effect: Z = 0.26 (P = 0.80)				

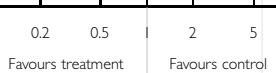
Analysis 1.3. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 3 Incidence of late deaths (> or = 30 days).

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 3 Incidence of late deaths (> or = 30 days)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Enoxaparin vs unfractionated heparin					
ESSENCE 1997	47/1607	57/1564		58.3 %	0.80 [0.55, 1.17]
Subtotal (95% CI)	**1607**	**1564**		**58.3 %**	**0.80 [0.55, 1.17]**
Total events: 47 (Treatment), 57 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.14 (P = 0.26)					
2 Nadroparin vs unfractionated heparin					
FRAXIS 1999	49/1166	41/1151		41.7 %	1.18 [0.79, 1.77]
Subtotal (95% CI)	**1166**	**1151**		**41.7 %**	**1.18 [0.79, 1.77]**
Total events: 49 (Treatment), 41 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.43)					
Total (95% CI)	**2773**	**2715**		**100.0 %**	**0.96 [0.73, 1.27]**
Total events: 96 (Treatment), 98 (Control)					
Heterogeneity: Chi^2 = 1.84, df = 1 (P = 0.17); I^2 =46%					
Test for overall effect: Z = 0.29 (P = 0.77)					



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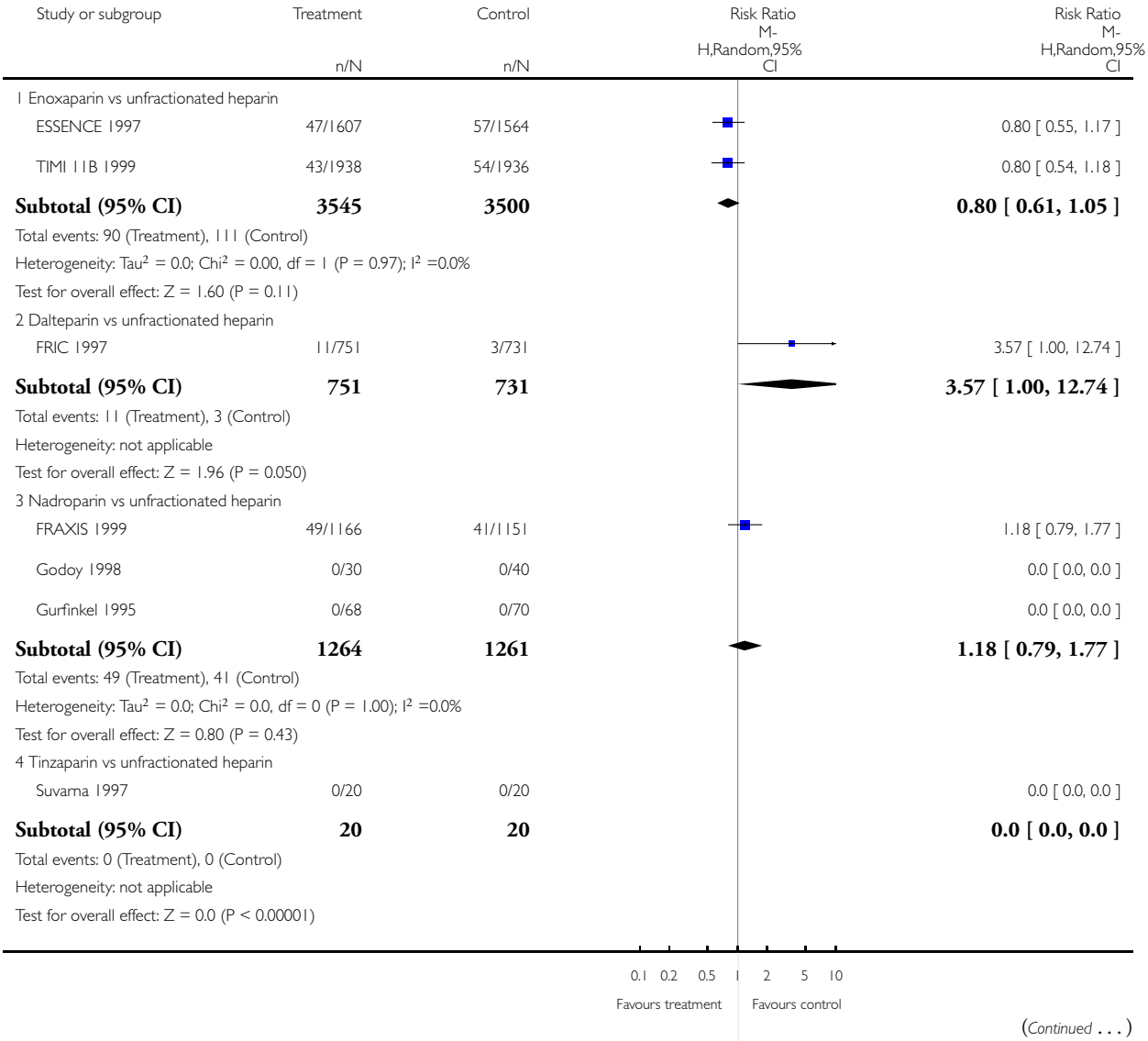
Analysis 1.4. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 4 Incidence of death over all periods.

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 4 Incidence of death over all periods



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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**5580**	**5512**		**1.00 [0.69, 1.44]**

Total events: 150 (Treatment), 155 (Control)

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 6.78$, df = 3 (P = 0.08); $I^2 = 56\%$

Test for overall effect: Z = 0.00 (P = 1.0)

Analysis 1.5. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 5 Incidence of early MI (< 48 hours).

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 5 Incidence of early MI (< 48 hours)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Enoxaparin vs unfractionated heparin					
ESSENCE 1997	11/1607	14/1564		27.2 %	0.76 [0.35, 1.68]
TIMI 11B 1999	26/1953	38/1957		72.8 %	0.69 [0.42, 1.12]
Total (95% CI)	**3560**	**3521**		**100.0 %**	**0.71 [0.47, 1.07]**

Total events: 37 (Treatment), 52 (Control)

Heterogeneity: $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 1.62 (P = 0.10)

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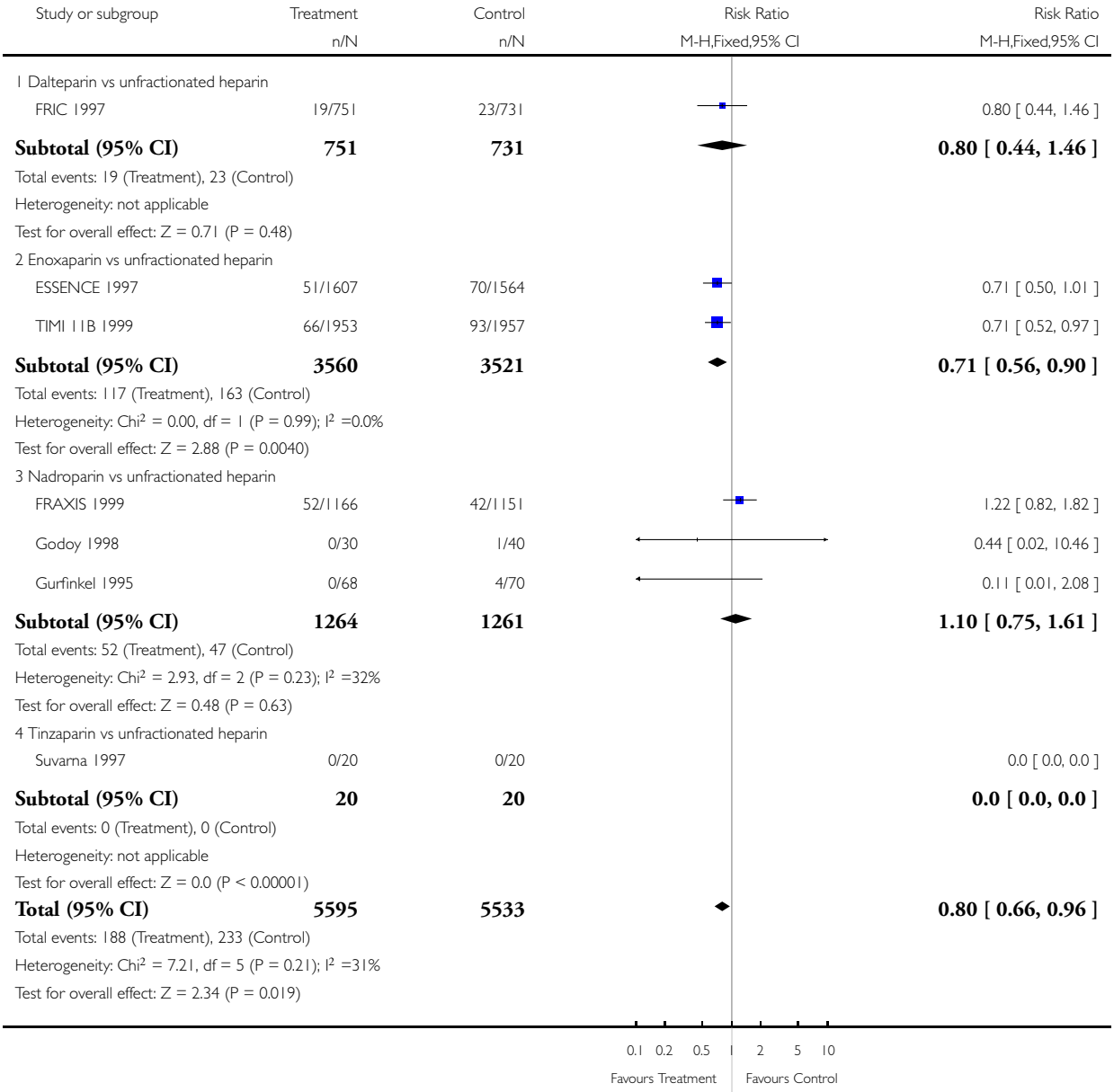
Analysis 1.6. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 6 Incidence of MI in sub-acute period (3-14 days).

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 6 Incidence of MI in sub-acute period (3-14 days)



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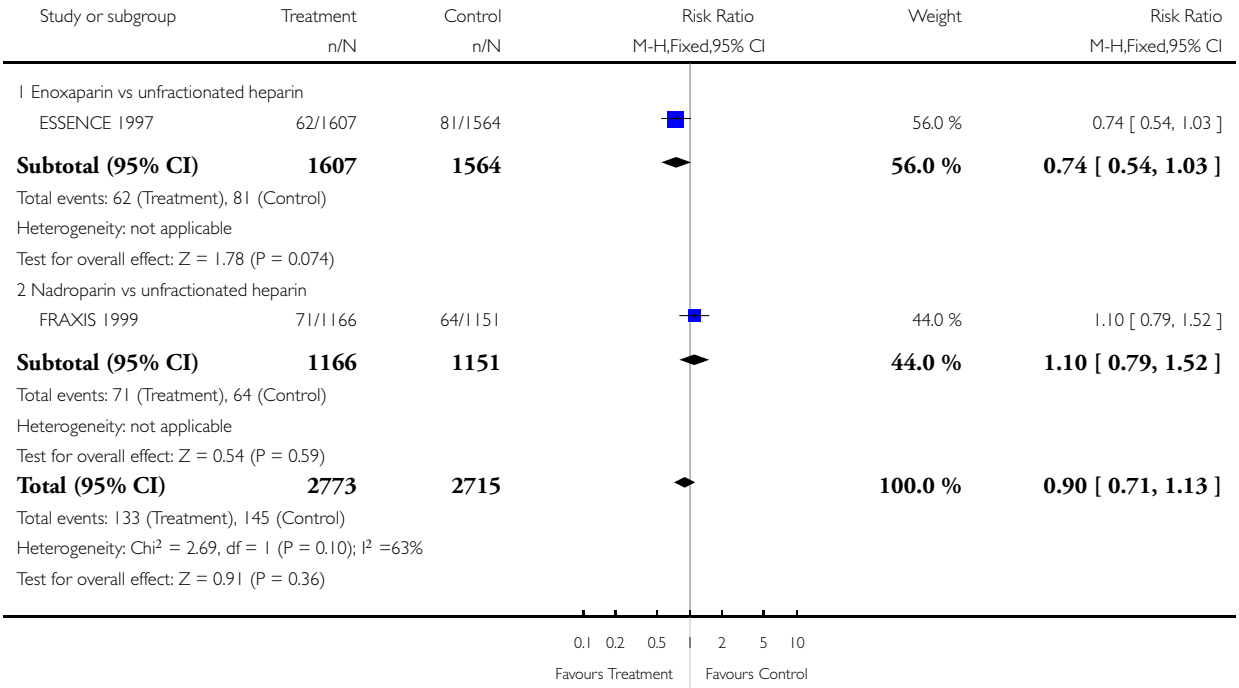
Analysis 1.7. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 7 Incidence of late MI (> or = 30 days).

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 7 Incidence of late MI (> or = 30 days)



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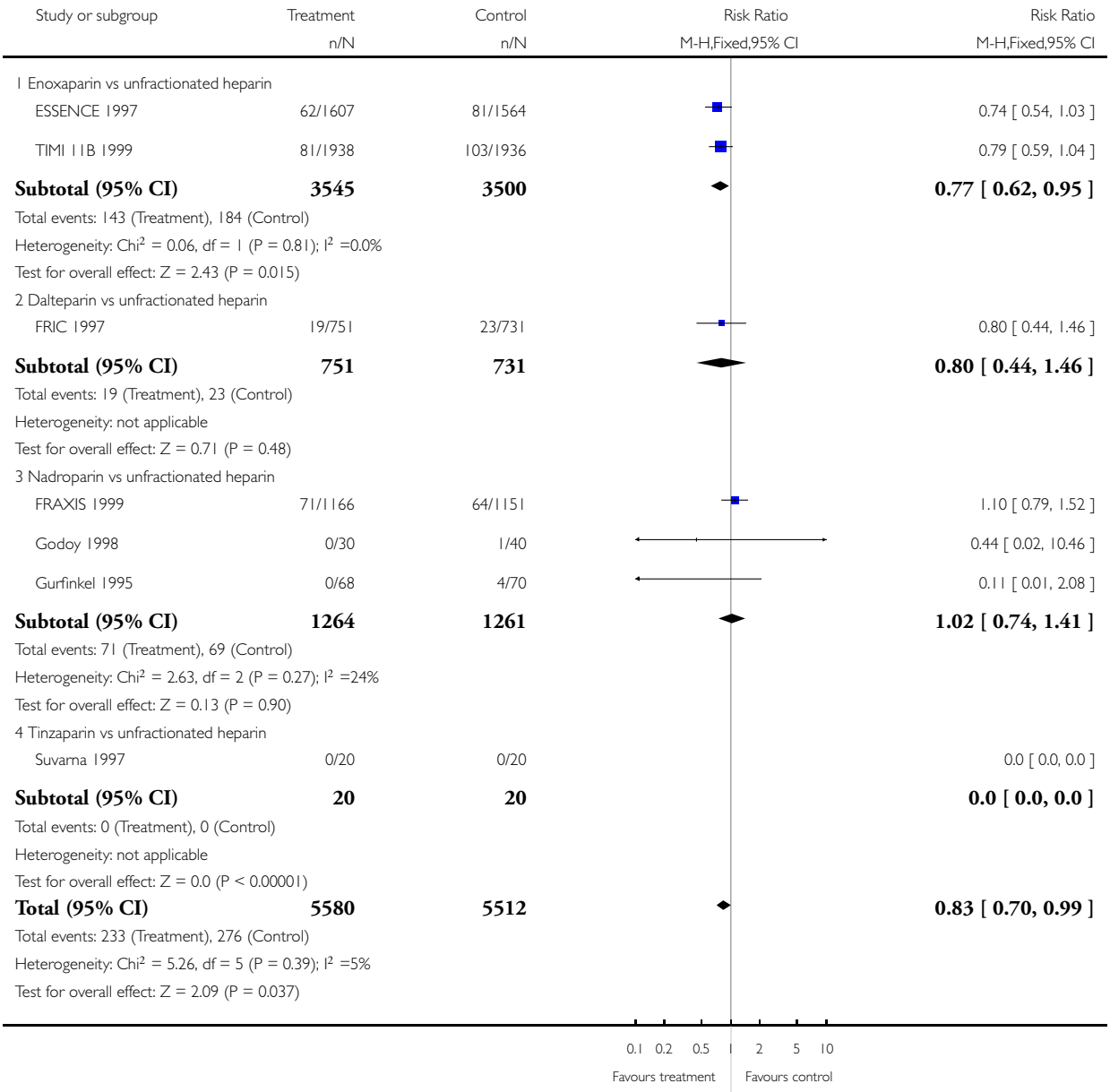
Analysis 1.8. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 8 Incidence of MI over all periods.

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 8 Incidence of MI over all periods



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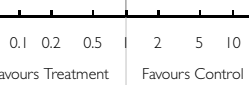
Analysis 1.9. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 9 Incidence of early recurrent angina (48 hours).

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 9 Incidence of early recurrent angina (48 hours)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Enoxaparin vs unfractionated heparin					
ESSENCE 1997	83/1607	99/1564		100.0 %	0.82 [0.61, 1.08]
Total (95% CI)	**1607**	**1564**		**100.0 %**	**0.82 [0.61, 1.08]**
Total events: 83 (Treatment), 99 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					



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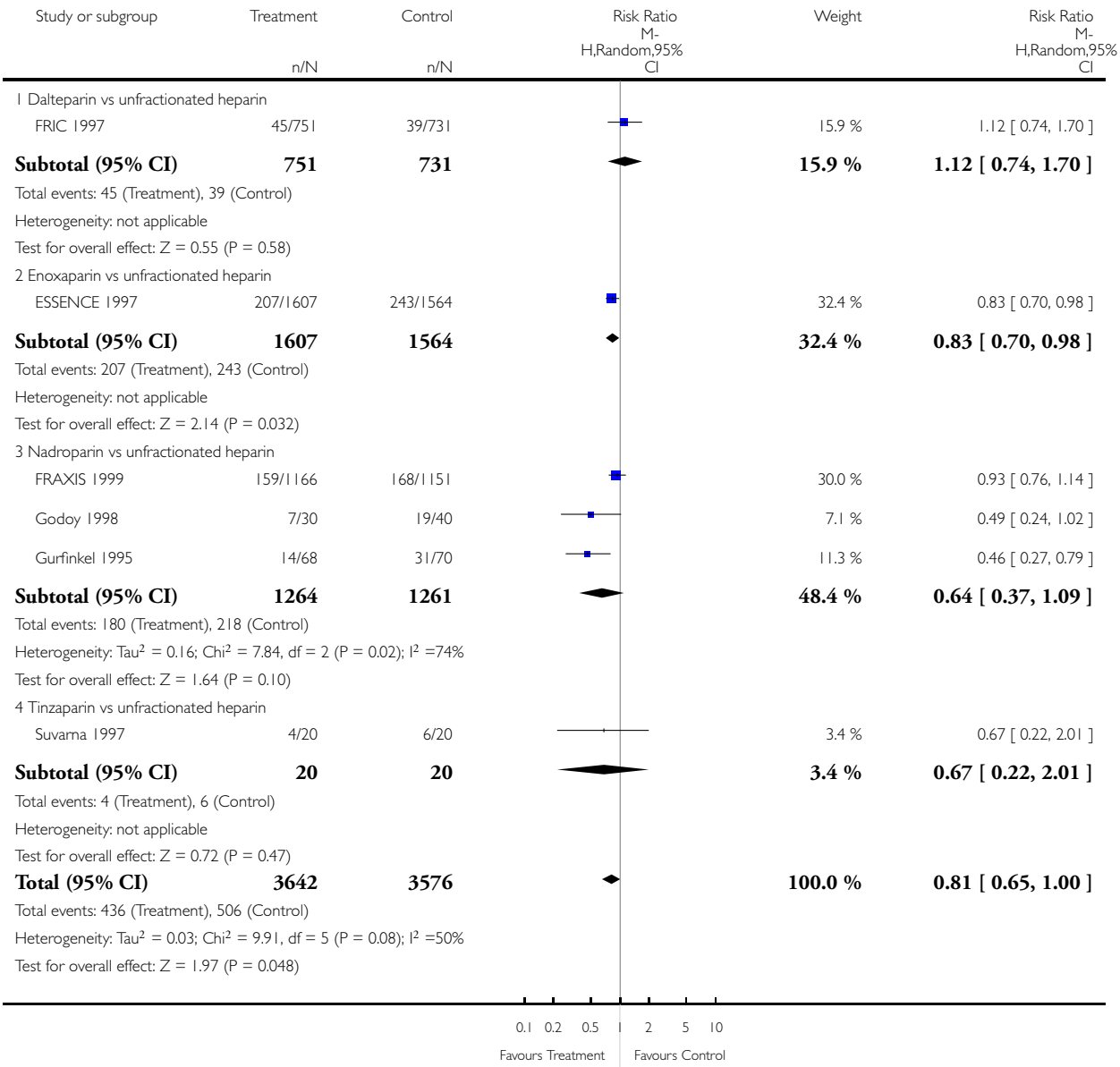
Analysis 1.10. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 10 Incidence of recurrent angina in subacute period (3-14 days).

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 10 Incidence of recurrent angina in subacute period (3-14 days)



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Analysis 1.11. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 11 Incidence of late angina (> or = 30 days).

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 11 Incidence of late angina (> or = 30 days)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Enoxaparin vs unfractionated heparin					
ESSENCE 1997	252/1607	281/1564		58.6 %	0.87 [0.75, 1.02]
Subtotal (95% CI)	**1607**	**1564**		**58.6 %**	**0.87 [0.75, 1.02]**
Total events: 252 (Treatment), 281 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.72 (P = 0.086)					
2 Nadroparin vs unfractionated heparin					
FRAXIS 1999	194/1166	200/1151		41.4 %	0.96 [0.80, 1.15]
Subtotal (95% CI)	**1166**	**1151**		**41.4 %**	**0.96 [0.80, 1.15]**
Total events: 194 (Treatment), 200 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.47 (P = 0.64)					
Total (95% CI)	**2773**	**2715**		**100.0 %**	**0.91 [0.81, 1.02]**
Total events: 446 (Treatment), 481 (Control)					
Heterogeneity: Chi^2 = 0.58, df = 1 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 1.61 (P = 0.11)					

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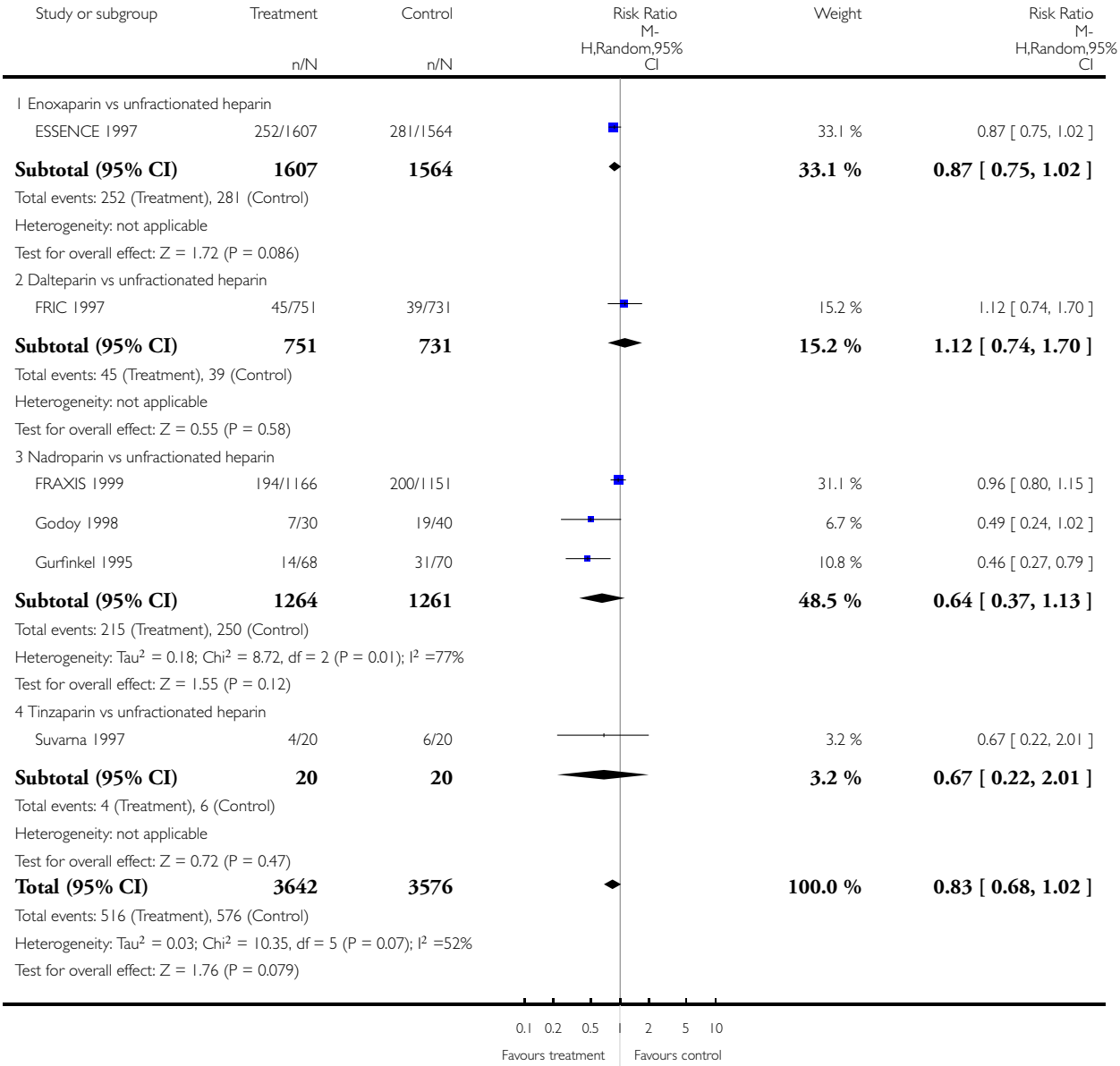
Analysis 1.12. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 12 Incidence of recurrent angina over all periods.

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 12 Incidence of recurrent angina over all periods



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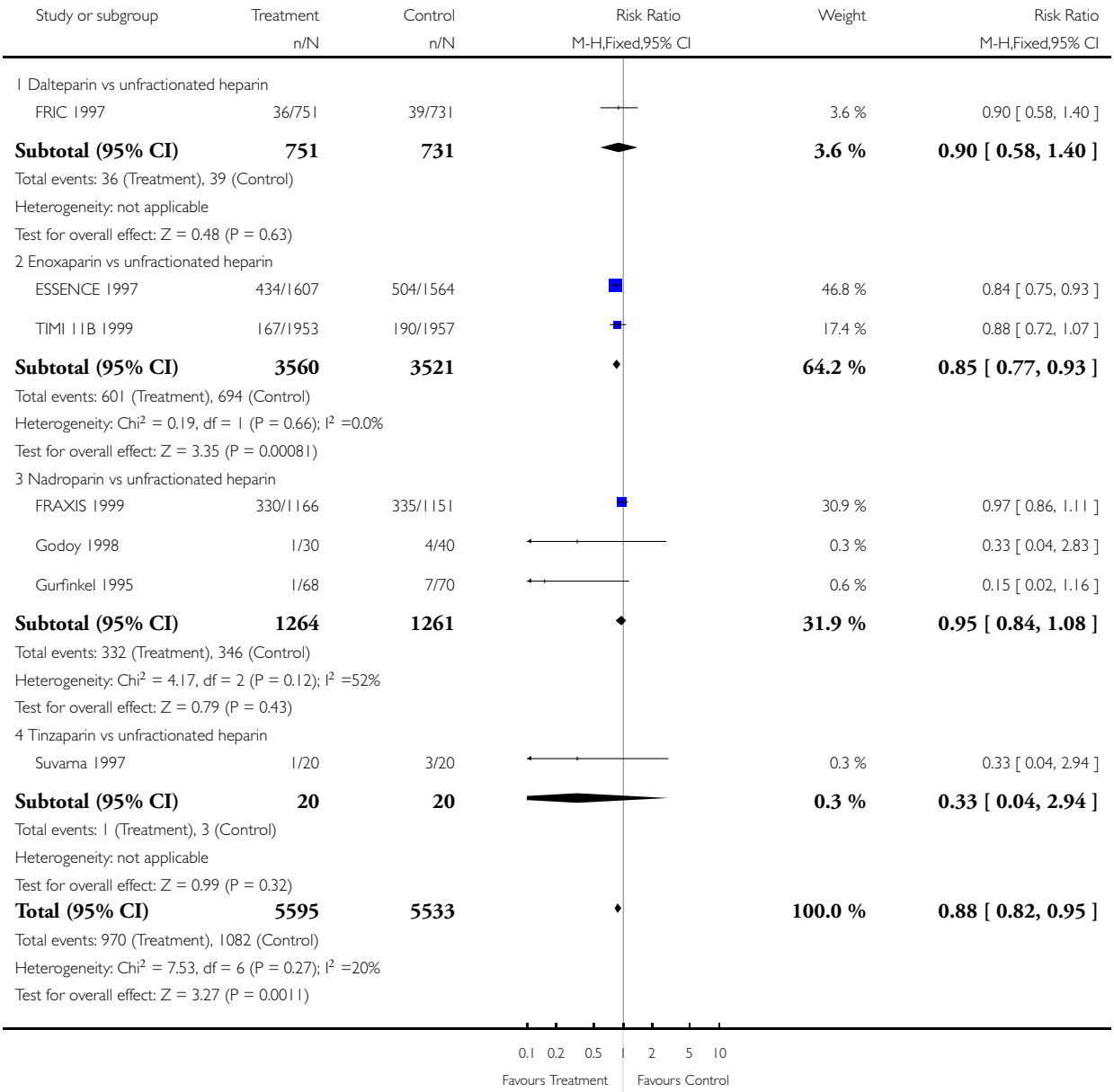
Analysis 1.13. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 13 Revascularization.

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 13 Revascularization



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Analysis 1.14. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 14 Multiple end point (< 48 hours).

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 14 Multiple end point (< 48 hours)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Enoxaparin vs unfractionated heparin					
ESSENCE 1997	99/1607	115/1564		46.6 %	0.84 [0.65, 1.09]
TIMI 11B 1999	108/1953	142/1957		53.4 %	0.76 [0.60, 0.97]
Total (95% CI)	**3560**	**3521**		**100.0 %**	**0.80 [0.67, 0.95]**
Total events: 207 (Treatment), 257 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.27, df = 1 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 2.52 (P = 0.012)					

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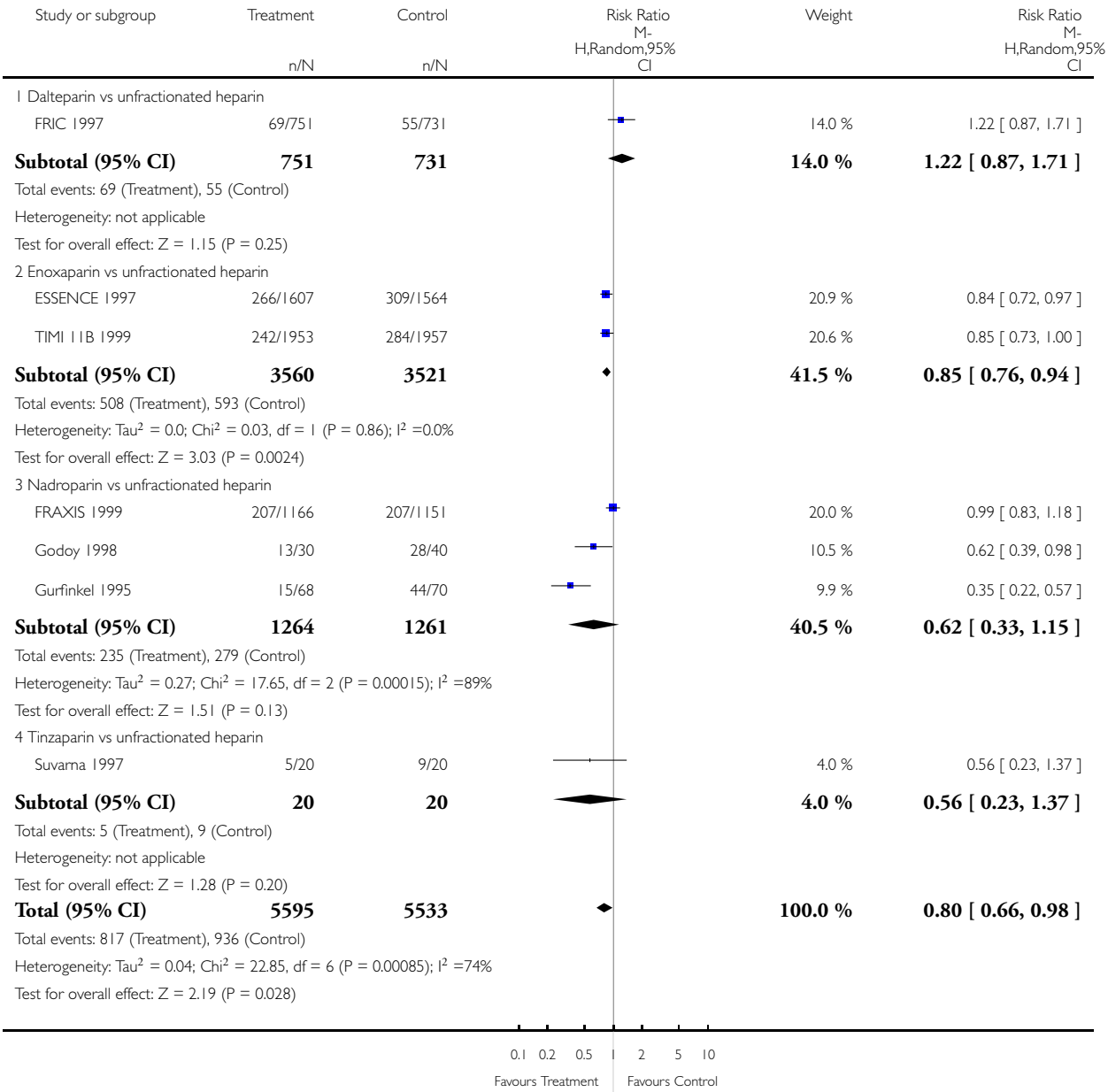
Analysis 1.15. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 15 Multiple end point events (3-14 days).

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 15 Multiple end point events (3-14 days)



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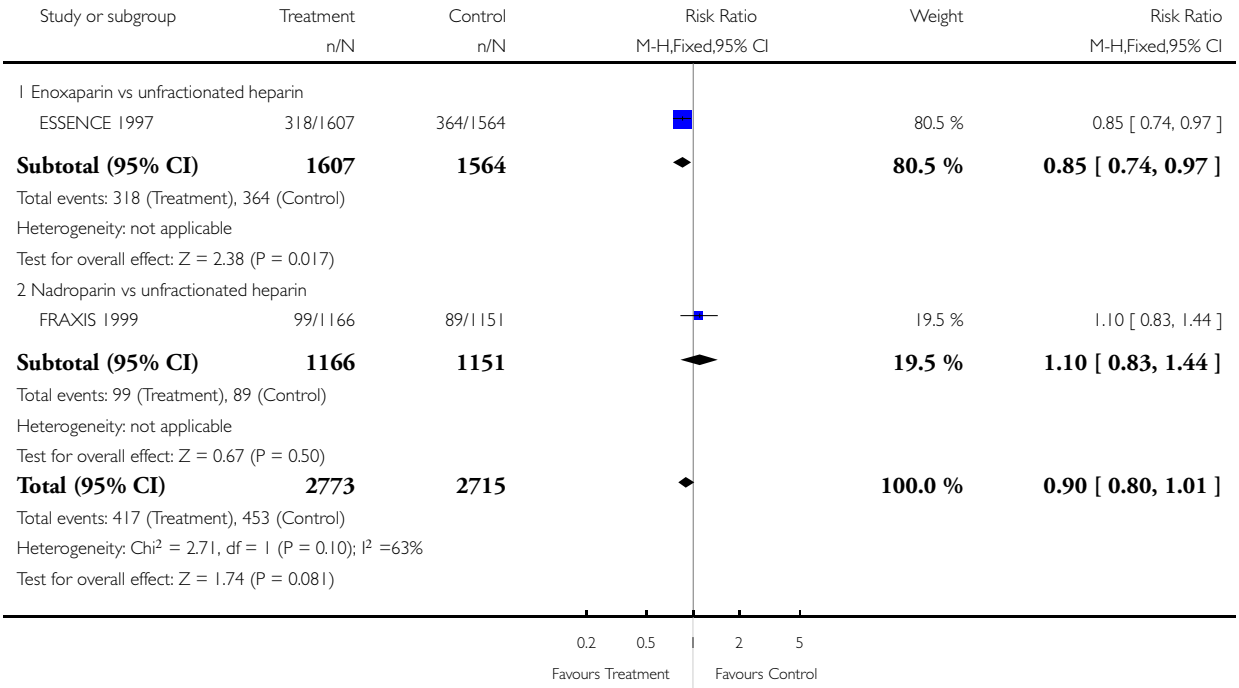
Analysis 1.16. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 16 Multiple end point events (> or = 30 days).

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 16 Multiple end point events (> or = 30 days)



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Analysis 1.17. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 17 Major bleeds.

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

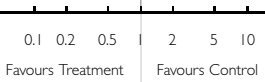
Outcome: 17 Major bleeds

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
ESSENCE 1997	102/1607	107/1564		0.93 [0.71, 1.21]
FRAXIS 1999	17/1166	18/1151		0.93 [0.48, 1.80]
FRIC 1997	8/751	7/731		1.11 [0.41, 3.05]
Gurfinkel 1995	0/68	2/70		0.21 [0.01, 4.21]
Suvarna 1997	0/20	0/20		0.0 [0.0, 0.0]
TIMI 11B 1999	29/1938	19/1936		1.52 [0.86, 2.71]
Total (95% CI)	**5550**	**5472**		**1.00 [0.80, 1.24]**

Total events: 156 (Treatment), 153 (Control)

Heterogeneity: Chi^2 = 3.52, df = 4 (P = 0.47); I^2 =0.0%

Test for overall effect: Z = 0.01 (P = 0.99)



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Analysis 1.18. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 18 Minor bleeds.

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 18 Minor bleeds

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ESSENCE 1997	188/1607	110/1564		1.66 [1.33, 2.08]
FRIC 1997	23/751	24/731		0.93 [0.53, 1.64]
Gurfinkel 1995	1/68	10/70		0.10 [0.01, 0.78]
Suvarna 1997	0/20	0/20		0.0 [0.0, 0.0]
TIMI 11B 1999	176/1938	48/1936		3.66 [2.68, 5.01]
Total (95% CI)	**4384**	**4321**		**1.40 [0.68, 2.90]**

Total events: 388 (Treatment), 192 (Control)

Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 32.20$, df = 3 ($P<0.00001$); $I^2 = 91\%$

Test for overall effect: Z = 0.91 (P = 0.36)

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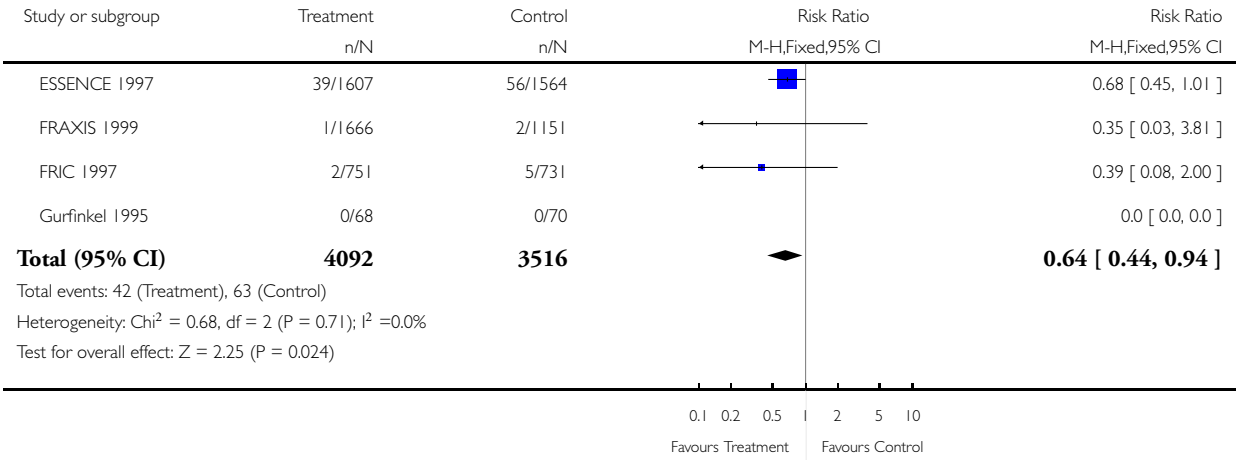
Analysis 1.19. Comparison 1 LMWH vs unfractionated heparin in acute coronary syndromes ., Outcome 19 Thrombocytopenia.

Review: Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Comparison: 1 LMWH vs unfractionated heparin in acute coronary syndromes .

Outcome: 19 Thrombocytopenia



F E E D B A C K

From David Cundiff: 15 February 2007

Summary

BACKGROUND

"... Despite weak evidence for the use of unfractionated heparin (UFH) for acute coronary syndromes, it is considered an accepted treatment for unstable angina and non-ST segment elevation myocardial infarction (MI)..."

Comment: The authors cited only two randomized controlled trials (RCTs) to justify the use of heparin in acute coronary syndromes (ACS). Theroux et al randomized 479 patients with unstable angina to aspirin (ASA), ASA + heparin, and placebo (1). No deaths occurred in the groups receiving ASA, whether they received heparin or not, while 3.3% of ASA + heparin patients had major bleeding compared with 1.7% of those receiving ASA alone (1). The "RISC Group" randomized 796 men with unstable coronary artery disease (unstable angina or non-Q-wave MI) to double-blind placebo-controlled treatment with oral aspirin 75 mg/day and/or 5 days of intermittent intravenous heparin (2). According to the abstract: "The risk of MI and death was reduced by aspirin. After 5 days the risk ratio was 0.43 (confidence intervals, 0.21-0.91), at 1 month 0.31 (0.18-0.53), and at 3 months 0.36 (0.23-0.57). Aspirin reduced event rates in non-Q-wave MI and unstable angina independently of electrocardiographic abnormalities or concurrent drug therapy. Heparin had no significant influence on event rate, although the group treated with aspirin and heparin had the lowest number of events during the initial 5 days."(2) In both trials, compared with ASA alone, heparin + ASA is evidence-based to increase major bleeding but not to reduce deaths or heart attacks.

No review has resulted from an important Cochrane protocol to evaluate the evidence for UFH for acute coronary syndromes by the same authors: K Magee, D Moher, B Rowe. Heparin versus placebo for acute coronary syndromes. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD003462. DOI: 10.1002/14651858.CD003462. (Protocol)

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If heparin doesn't work compared with placebo for acute coronary syndromes, as the above two RCTs suggest, there would be no need to do the subsequent comparison of heparin with low molecular weight heparins (LMWH).

IMPLICATIONS FOR PRACTICE

"This systematic review of randomized controlled trials supports the use of subcutaneous LMWH in the early treatment of acute coronary syndrome..."

Comment: Since heparin therapy (the control group) is not evidence-based to benefit morbidity or mortality in ACS, this conclusion is not warranted and should be revised. Both heparin and LMWHs are evidence-based to cause significant iatrogenic morbidity and mortality in ACS. Neither is evidence based to reduce morbidity or mortality.

IMPLICATIONS FOR RESEARCH

The authors do not recommend RCTs with ASA with a LMWH versus ASA alone. Given the lack of evidence supporting either UFH or LMWH, this would be the only trial that would be appropriate to consider.

References

(1) Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. New England Journal of Medicine. 1988;319:1105-1111.

(2) Risk of myocardial infarction and death during treatment with low-dose aspirin and intravenous heparin in men with unstable coronary artery disease. The RISC Group. Lancet. 1990;336:830-837.

Reply

Dr. Cundiff raises legitimate concerns in his letter. If there is no evidence supporting the benefit of UFH in the treatment of ACS then why compare LMWH to UFH? At the time the review was initially conducted, UFH was the standard practice for the treatment of ACS as recommended by the AHA/ACC. We wanted to compare the newer treatment modality, LMWH, against the current standard of care. Having completed this review, we then asked the same question asked by Dr. Cundiff: What is the evidence for the use of any heparin in the treatment of ACS? To answer this question, we submitted the protocol for the systematic review that Dr. Cundiff cites in his letter: K Magee, D Moher, B Rowe. Heparin versus placebo for acute coronary syndromes. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD003462. DOI: 10.1002/14651858.CD003462. Protocol. (Heart)

It is anticipated this review will be published by the end of 2007. In the meantime, I would refer to the conclusions reached by this unpublished review:

We identified 59 potentially relevant studies, 8 of which (3110 participants) were included in this review. We found no evidence for difference in overall mortality between the groups treated with heparins compared to placebo (RR = 1.01; 95% CI: 0.43, 2.38). Heparins reduced the occurrence of MI (RR = 0.45; 95% CI: 0.30, 0.67). We found no evidence for difference in occurrence of recurrent angina (RR = 0.81; 95% CI: 0.60, 1.09), revascularization procedures (RR = 0.93; 95% CI: 0.76, 1.15), major bleeds (RR = 2.05; 95% CI: 0.91, 4.60), or thrombocytopenia (RR = 0.20; 95% CI: 0.01, 4.24). More patients treated with heparins experienced minor bleeds (RR = 6.80; 95% CI: 1.23, 37.49). From these results, 37 patients need to be treated with heparin to prevent 1 additional MI. As a sub-group, patients treated with LMWH experienced a lower incidence of MI, recurrent angina and required fewer revascularization procedures.

In essence, all heparins reduced the occurrence of MI and were associated with more minor bleeds compared to placebo. As a subgroup, the positive effects were more pronounced with LMWHs. This supports the results and conclusions of the systematic review comparing LMWH to UFH for the treatment of ACS.

Contributors

David Cundiff

Kirk Magee

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From David Cundiff, 22 July 2008

Summary

I thank Dr. Magee for the reply.

The Plain language summary states: "The review of trials found that UFH and LMWH were equally effective in preventing death" Consider changing this statement to "equally ineffective in preventing death" As you noted in your reply to my first feedback letter, "We found no evidence for difference in overall mortality between the groups treated with heparins compared to placebo (RR = 1.01; 95% CI: 0.43, 2.38)".

The appropriateness of this review is predicated on the efficacy of heparins when compared with placebo where all subjects are also treated with aspirin. The authors maintain that their recently published Cochrane Review of this topic establishes the benefit of a heparin plus aspirin versus aspirin alone. I dispute that contention (See my feedback letter for Magee K, Moher D, Rowe B. Heparin versus placebo for acute coronary syndromes. Cochrane Database of Systematic Reviews. Art. No.: CD003462. DOI: 003410.001002/14651858.CD14003462.) While Magee et al did partition the events by duration of follow up with an intention to treat analysis, they inappropriately based the conclusion of the review on the difference in Mis while subjects were still taking heparin. This heparin versus placebo review did not account for events (MIs and reactivation of angina) related to rebound hypercoagulability after discontinuing heparin. Had the conclusion been based on the comparison of adverse events at least a week after the heparin was stopped, no benefit would have been found.

Neither LMWHs or UFH are evidence-based to be beneficial for people with acute coronary syndrome, so comparing them is inappropriate. With additional antiplatelet agents and invasive procedures in recent years, heparins are significantly more hazardous than when the trials in this review were done. These drugs should not be used for acute coronary syndrome outside of a placebo-controlled RCT.

Contributors

David Cundiff

WHAT'S NEW

Last assessed as up-to-date: 31 October 2002.

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 July 2008. The Cochrane Heart Group apologises for the delay

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 1, 2003

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Date	Event	Description
9 September 2008	Amended	Converted to new review format.
11 May 2007	Feedback has been incorporated	Feedback and author response added
1 November 2002	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. Primary author.

Sevcik W: Protocol development, grant writing, translation, and editing manuscript.

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.

DECLARATIONS OF INTEREST

The authors who have been involved in this review have done so without any known conflicts of interest. They are not involved with the primary studies in this systematic review. The Division of Emergency Medicine, University of Alberta and Dr. Rowe have received funding from several makers of the LMWH (e.g. Pharmacia, Aventis, Sanofi) for educational and research purposes, but none of the staff are paid consultants of any pharmaceutical company that produces LMWH.

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Internal sources

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- Department of Emergency Medicine, Dalhousie University, Halifax, Canada.

External sources

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- Canadian Institute of Health Research (CIHR); Canada Research Chairs Program (BHR), Canada.

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INDEX TERMS

Medical Subject Headings (MeSH)

Angina, Unstable [*drug therapy]; Anticoagulants [adverse effects; *therapeutic use]; Fibrinolytic Agents [adverse effects; *therapeutic use]; Heparin [adverse effects; therapeutic use]; Heparin, Low-Molecular-Weight [adverse effects; *therapeutic use]; Injections, Intravenous; Injections, Subcutaneous; Myocardial Infarction [*drug therapy]; Randomized Controlled Trials as Topic; Syndrome

MeSH check words

Humans

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