University of Alberta

Heparins in the early treatment of acute coronary syndromes

by

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Dedication

This thesis is dedicated to the memory of my father, Carroll M. Magee. Though never a scholar, he was and continues to be an ever present source of inspiration in my life.

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List of Abbreviations

ACS	Acute coronary syndrome
aPTT	Activated partial thrombplastin time
ASA	Acetylsalicylic acid
95% CI	95% confidence limits
CRG	Cochrane review group
ED	Emergency department
HIT	Heparin induced thrombocytopenia
I^2	Heterogeneity statistic
k	Kappa
LMWH	Low molecular weight heparin
MI	Myocardial infarction
NSTEMI	Non ST-segment elevation myocardial infarction
OR	Odds ratio
P	p-value
RCT	Randomized controlled trial
RevMan	Review Manager, 4.01 software program
SMD	Standardized mean differences
TF	Tissue factor
UA	Unstable angina
UFH	Unfractionated heparin
WMD	Weighted mean differences

Chapter One

Introduction

1.1 Acute coronary syndromes: definition, description of the problem, and treatment approach

Acute coronary syndromes (ACS) represent a clinical spectrum of disease from non-ST segment elevation myocardial infarction(NSTEMI) to unstable angina (UA). Pathophysiologically, the signs and symptoms are created by atherosclerotic plaques and endovascular thrombus formation. Atherogenesis starts early in childhood and manifestations of the disease take decades to develop. These manifestations include: mature plaques responsible for ischemic heart disease, cerebral vascular accidents, aortic aneurysms and intermittent claudication. Mature plaques consist of a soft, lipid-rich atheromatous "gruel" and a hard, collagen-rich sclerotic tissue. Although the sclerotic component composes nearly 70% of the average stenotic coronary artery plaque, it is the atheromatous gruel that is the most dangerous component.(1)

When the plaque fractures or ruptures, the highly thrombotic atheromatous core is exposed to flowing blood and the coagulation cascade is initiated. Tissue factor (TF) in the lipid rich core complexes with factor VIIa which promotes the generation of factor Xa. The effects of factor Xa are greatly multiplied downstream resulting in the production of large quantities of thrombin. Ultimately, fibrin strands are deposited and platelets are activated, migrating to the area in an attempt to heal the damaged vessel. As the coronary artery

becomes occluded, myocardial oxygen demand exceeds supply at a cellular level. This pathophysiological change results in ischemia, which may progress to myocardial infarction.

The recognition of the increasingly important role of inflammation in the pathogenesis of atherothrombotic vascular events challenges our historic understanding of this disease process. Macrophage infiltration of plaque is central to this process.(2) Research of the inflammatory process may identify novel approaches to risk stratification and new therapeutic strategies.

Clinically, patients with ACS often experience chest pain, which is commonly associated with other symptoms, such as dyspnea, diaphoresis, weakness/pre-syncope, and/or nausea. These symptoms are reported variably in patients with ACS, and some patients may present without the cardinal feature of chest pain. A high index of suspicion is required to make the diagnosis in such settings, and often times is based on risk factor assessment in addition to clinical presentation.

At the bedside, UA and NSTEMI may have identical clinical presentations. UA refers to chest pain which is ischemic in origin, yet not designated as an acute infarction by changes in ECG or cardiac enzymes. NSTEMI constitutes a syndrome which may be differentiated from UA by the presence of elevated cardiac enzymes indicating actual myocardial necrosis and infarction. The term NSTEMI replaces the older nomenclature of non-Q-wave MI and will be used throughout this manuscript.

Epidemiology of ACS:

Acute coronary syndromes are potentially life threatening disorders which commonly require emergency medical care as well as hospitalization. The National Center for Health Statistics reports 1,433,000 hospitalizations for UA or NSTEMI in the United States in 1996.(3) The Emergency Department (ED) is often the initial point of contact with the health care system for these patients. In 1997, there were 5,315,000 ED visits in the United States for patients experiencing chest pain or related symptoms.(4) In Alberta in 2000, there were 1.7 million ED visits of which ACS accounted for 11,023 visits (0.65%). This represents an ED presentation rate for Alberta residents with ACS of approximately 4 per 1,000 persons.(5)

Cost of ACS:

Patients with ACS do not represent a single point contact with the medical system. The majority of these patients will be admitted to hospital upon initial presentation and approximately 28% of these patients will require a repeat hospital admission within the first year.(6) The direct medical costs for treating patients with ACS in the United States are over $51 billion a year. Adjusting for lost productivity due to mortality and morbidity, the cost to society has been estimated at $95 billion. In 1990, a total of 2.9 million hospital days were used by patients with UA.(7) With our aging population, the direct costs of coronary care will increase faster than might be expected by the prevalence of coronary artery disease itself.

Drug costs are the fastest growing sector in health care. In Canada, there has been a substantial increase in both the utilization and expenditures for cardiovascular medications.(8) Despite the abundance of positive RCTs in the cardiology literature, one review of 4 major drug trials estimated that only 9 out of 100 patients actually benefited from receiving them.(9) There is a need not only to search for new therapies, but to also better define which patients will most benefit from existing therapies.

ACS Management Approach

Most patients with symptoms suspicious for ACS will either present to the ED on their own or via ambulance. Initial assessment usually includes history and physical examination, laboratory investigation, radiography, and electrocardiography (ECG). The differential diagnosis for patients with undifferentiated chest pain is broad, including non-ischemic disease such as pneumothorax, pneumonia, pulmonary embolism or infarction, acute myocardial infarction, dissection, chest wall pain, and a range of other problems. Physicians use diagnostic reasoning, test results and clinical acumen to rule-in or rule-out these disorders.

Treatment of ACS is generally aimed at reducing myocardial oxygen demand while maximizing arterial oxygen supply. Anti-ischemic therapy includes the use of oxygen, morphine, nitroglycerin, β-blockers, and calcium channel antagonists.(10) In patients with signs of respiratory distress or arterial hypoxemia, oxygen administration to maintain arterial oxygen saturation greater than 90% will improve oxygen supply to the myocardium. Nitroglycerine

(intravenous, sublingual, and skin application) affects both oxygen supply and demand. By dilating the venous bed, it increases venous pooling which decreases myocardial preload, a direct determinant of myocardial oxygen use. Nitrates also dilate normal and atherosclerotic coronary arteries thereby, improving blood flow to the myocardium. Morphine's potent analgesic and anxiolytic effects reduce myocardial oxygen demand by inhibiting the release of stimulatory sympathetic catecholamines. β-blockers competitively block adrenergic receptors in the myocardium, decreasing heart rate and contractility as well as lowering the systolic blood pressure. These actions combine to decrease cardiac work and myocardial oxygen demand.

Calcium channel blockers are used in patients already receiving nitrates and β-blockers who continue to be symptomatic. They have variable effects including vasodilatation, decreasing myocardial contractility and heart rate. This is thought to be beneficial in decreasing myocardial oxygen demand and improving myocardial blood flow.

Anti-platelet and anticoagulant therapy in ACS

Anti-thrombotic and anti-platelet therapies provide specific treatments for ACS and will be discussed in detail below. Perhaps the strongest evidence of efficacy exists with regard to acetylsalicylic acid (ASA) anti-platelet therapy.(11) ASA irreversibly inhibits cyclooxygenase-1 within platelets which reduces platelet aggregation. The newer thienopyridines (e.g., ticlopidine and clopridogrel) have been suggested for patients who can not safely tolerate ASA therapy. These

agents should, however, be used with caution given the significantly greater risk of bleeding associated with their use.(12)

Unfractionated heparin (UFH) has been the traditional anticoagulant treatment of choice for ACS and other cardiac disorders. Low molecular weight heparins (LMWH), direct thrombin inhibitors such hirudin and most recently the glycoproptein IIb/IIIa inhibitors have stimulated renewed interest in this arm of therapy.(13)

1.2 Heparins in ACS

The use of intravenous heparin for the acute management of unstable angina/non-STEMI was first introduced in 1982.(14) The perceived benefit of adding UFH to ASA was such that it quickly became the "standard of care" and was soon endorsed by national authoritative bodies.(10) UFH, however, was not a panacea. Evidence for its benefit was weak (15) and clinicians have long been familiar with the practical difficulties of heparin administration. The dose response curve was unpredictable and coagulation parameters had to be frequently monitored resulting in repetitive, costly and painful blood draws and laboratory testing. Additionally, it was difficult to keep coagulation parameters within the therapeutic range.

This is due the molecular chemistry of UFH. Unfractionated heparin is a heterogeneous mixture of polysaccharide chains with a mean molecular weight of 15,000. Its mechanism of action is mediated through a unique pentasaccharide with a high affinity for antithrombin III (ATIII). This bond

produces a conformational change in ATIII which increases its ability to inactivate thrombin, factor Xa and factor IXa. Of the three, thrombin is the most sensitive to inhibition by UFH. However, only one third of the heparin molecules have ATIII-mediated anticoagulation activity dependant on their chain length. As well, clearance of UFH is influenced by its molecular weight. These, in addition to its non-specific binding to proteins and cells, may explain some of the clinical limitations of UFH.(16)

In this light, researchers have sought newer agents which might overcome these short-falls. Low molecular weight heparin is derived the depolymerization of standard UFH into lower-molecular weight fragments with a mean weight of 4,000 to 5,000. Theoretically, LMWH has a number of advantages compared to UFH: (1) unlike UFH which is active against several different factors, LMWH primarily inhibits factor Xa; (2) reduced non-specific binding to plasma proteins and less sensitivity to inactivation by platelet factor 4 translates to a more predictable dose-response curve; (3) less binding to macrophages resulting in a longer half-life; (4) reduced binding to platelets which may explain the observed lower incidence of heparin induced thrombocytopenia (HIT). Practically, this translates into several features which make LMWH very attractive for clinical use. The longer half-life means that LMWH can be given as intermittent injections instead of continuous intravenous infusions. A predictable dose-response anticoagulation effect negates the need for the careful laboratory monitoring that was the hallmark of UFH.(17) An improved safety profile (less major and minor bleeding, less HIT, etc.) adds further to the desirability of use. Finally, as

pressure mounts to rationalize healthcare expenditures, one must consider the economic impact of introducing novel therapies. Although the per unit cost of LMWH is higher than UFH, an economic analysis must also account for the attendant costs of administration and laboratory monitoring as well as the "downstream" costs of further treatment such as the need for revascularization procedures. When these factors are taken into consideration, some suggest a net cost savings for LMWH over UFH in the treatment ACS.(18)

1.3 The clinical questions

As if often the case, clinical medicine has out-paced a careful examination of the existing evidence. Would adult patients presenting to the hospital with ACS benefit from the addition of any heparins (UFH or LMWH) to standard therapy? If so, do the theoretical advantages of LMWH over UHF translate into clinically significant improvements to patient outcomes?

1.4 The role of a systematic review

In order to answer these questions, several avenues are open to the clinician. He/she may elect to comprehensively search the current literature and critically appraise the relevant articles. With the never-ending abundance of clinical questions which arise in daily practice, this time consuming effort quickly enters the realm of impossibility. Perhaps the most common approach, one may search for and use a traditional narrative review. There are many biases associated with narrative reviews, the most common of which are selection and

publication bias. Reliance on narrative reviews is further problematic due to other methodological errors. Other options may include using recommendations of experts in the field or evidence-based clinical practice guidelines.(19,20) The final option is to look for a systematic review or a meta-analysis which examines the clinical problem in question.

Chalmers and Altman have defined a systematic review (SR) as "a review that has been prepared using a systematic approach to minimising biases and random errors which is documented in a materials and methods section".(21) The synthesis of results may be simply qualitative, summarizing and critiquing the methods of the primary studies. The authors may, however, attempt to statistically analyze the results from the independent studies to produce a single summary estimate of the treatment effect – hence the term meta-analysis. While it is always desirable to conduct a systematic review, the decision to statistically pool the results from separate studies in the form of a meta-analysis is more controversial and may even be inappropriate in certain circumstances.(22)

In essence, a systematic review is an observational study of the existing evidence.

Getting started: Similar to other areas of research, a detailed protocol must be formulated *a priori* in order to minimize bias. The first step in this process requires the formulation of an explicit research question. The patient population, the interventions of interest, the comparison, and the outcomes to be studied (the so called PICO methodology) must be clearly stated. The ***topic area*** for the SR must be congruent with the PICO and these designations then

dictate the ***study design*** (a.k.a. level of evidence) required for searching. For example, in therapy reviews, randomized controlled trials are the highest level of evidence upon which to base clinical decisions and, consequently, they should be the study design of preference for the review.

Searching: Systematically searching the existing literature for relevant trials is at the heart of any systematic review. The search strategy should be clearly delineated and should not be limited to English language and published articles. High-quality systematic reviews employ rigorous attempts to uncover unpublished trials as their results may systematically differ from published trials. This may include contacting colleagues, experts in the field, and representatives of the pharmaceutical industry and authors of primary studies. Registers such as the Cochrane Collaboration's Register of Registers and the internet based *meta*Register of Controlled Trials may be valuable sources of information.(23) Since a large proportion of controlled trials are only published as meeting abstracts, and as the results are often different from those later published as full manuscripts, databases such as the System for Information on Grey Literature in Europe (SIGLE) and the British Library's "Inside" database are an important source for this "grey literature".(24)

Selection: To minimize selection bias, explicit inclusion/exclusion criteria should be well described. Having two reviewers decide on the eligibility of considered studies reduces the degree of subjectivity and reduces selection bias. Although randomized controlled trials provide the best evidence of therapeutic efficacy and effectiveness, other designs may be used in SRs. For example,

"pseudo RCTs" refers to trials in which the individuals were assigned prospectively to one of two (or more) alternative treatment groups in a manner that was intended to be unbiased. These quasi-RCT methods of randomisation include, but are not limited to alternation, date of birth, or case record number.(24)

Study Quality: methodological limitations of individual studies will greatly affect the outcomes. Standardized scoring systems allow reviewers to objectively assess the quality of trials.(25) Sensitivity analysis can then be conducted to determine the effect of study quality on the outcomes of the review.

Data Collection: After the studies have been selected for inclusion in the review, the reviewer must abstract the data using a standardized methodology.

Pooling and Heterogeneity: The reviewer must decide whether it is appropriate to pool the results of individual trials to obtain an overall summary result. Combining data from across trials may provide the sample size necessary to reach firmer conclusions about treatment effects that were not readily apparent from smaller studies with non-statistically significant results. The decision to pool data starts with the selection of the research topic. For example, by obtaining studies that employ the same PICO and design, high-quality SRs are to some degree reducing potential heterogeneity. Further decisions on pooling will be based on whether or not significant heterogeneity between the study results is identified (visually or statistically). In addition to defining potential sources of heterogeneity when developing the review protocol and visually inspecting a Forest plot, statistical tests such as Cochran's chi-squared test for

homogeneity(26) and Higgins' I-squared (I^2) statistic(27) may indicate the extent of heterogeneity. Differences in trial design, lack of appropriate trials and discordant results may all contribute to heterogeneity and suggest recommendations for future research.

Sensitivity and Subgroup analyses: The robustness of the findings of a meta-analysis should always be scrutinized with sensitivity analyses. This should include an assessment of the influence of the methodological quality of the included studies on the final results. Similar to sub-group analysis in trials, meta-analytic sub-group analysis must be approached with caution as they are prone to bias. Although systematic reviews offer a firmer foundation for conducting sub-group analysis, they may still produce findings which are potentially misleading.(28)

Evidence Translation: A rigorously conducted systematic review has the potential to offer the "best evidence" for treatment effect and whether these findings can be generalized across patient populations and treatment settings.(29) Systematic reviews can also identify areas in need of further research. In fact, some have recommended that a systematic review of the known evidence should be conducted prior starting any clinical trial (30) to determine the presence of equipoise. Furthermore, others have suggested that new clinical trials should incorporate their results into up-to-date systematic reviews so that readers can better assess the impact of the results in the light of current related evidence.

1.5 The Cochrane Collaboration

In his 1972 book, "Effectiveness and efficiency. Random reflections on health services"(31) the British epidemiologist Archie Cochrane recognized that health care professionals wish to make informed decisions about patient care but lacked ready access to reliable reviews of the evidence in the literature. In response to this call to arms, the British National Health Service provided funding to establish a "Cochrane Centre" which was eventually opened in Oxford, England in 1992.(32) By 1993, the Cochrane Collaboration was formally established at the first annual Cochrane Colloquium. The mandate of this international, independent, non-profit organization is to provide high quality, up-to-date, accurate information about the effects of healthcare worldwide. It produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions.(33)

The Cochrane Collaboration ensures the production of high quality systematic reviews by following a rigorous and now well-established protocol. First, authors must indicate their intention to complete a review and submit a protocol prior to commencing a review. This prevents duplication of reviews and ensures that methods are defined *a priori*. Next, there must be a well-defined clinical question with specific criteria for determining which trials will be included in the final analysis. Publication and selection bias are both addressed and rigorous and comprehensive search strategies not limited by language

restrictions are developed. Quality assessment, appropriate pooling, sub-group and sensitivity analyses are further addressed in Cochrane reviews.(34)

The Cochrane Collaboration provides support for individuals in variety of ways. Support staff from Collaborative Review Groups (CRG) provide assistance with searching the literature, retrieving articles, translation of foreign language studies and statistical methods. Local, national and international workshops provide hands-on training in the methodologies of conducting a systematic review. The Collaboration also produces a free software package (RevMan) developed for analyzing and reporting reviews. Quality is assured through a peer-review process as rigorous at that for traditional medical journals (35); two editors within the CRG and at least one external review by an expert in the field. Once completed, reviews are published electronically by Update Software in the Cochrane Library under the Cochrane Database of Systematic reviews. This is updated quarterly and authors are encouraged to regularly update reviews to include new research. In comparison to reviews published in paper-based journals, Cochrane reviews have better methodological rigour; they more often include a description of inclusion/exclusion criteria and assess trial quality. As well, they are updated more frequently.(36)

1.6 The proposal

Searching the literature for evidence for the use of heparins in the acute treatment of ACS revealed several relatively small relevant clinical trials with equivocal results had been published in this area. A systematic review published

in 1996(15) reported on 6 trials comparing heparin to placebo and concluded that patients with unstable angina treated with heparin had a "33% reduction in risk of MI or death" despite the fact that confidence interval crossed the null value. Largely based on this study, heparin has been incorporated as the standard of care for the treatment of unstable angina and non-STEMI and the benchmark against which newer anti-thrombin treatments are judged.

To address the question of the use of heparins in the early treatment of ACS, two systematic reviews have been prepared for this thesis. The first review revisits the basic role of heparin in addition to standard therapy compared to placebo in the acute management of unstable angina and non-STEMI. In light of more recent advances in anti-thrombin therapy, the search for evidence has been broadened from that of previous reviews to include both UFH and LMWH. The second systematic review expands on this theme to answer the question whether there is an efficacy difference between UFH and LWMH in the acute management of ACS. Both reviews examine the impact of these therapies on mortality, MI, recurrent angina, urgent revascularization procedures as well as on some of their potential complications including major and minor bleeding and thrombocytopenia.

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Chapter Two

Heparins versus placebo for acute coronary syndromes

2.1 Introduction

Unstable angina (UA) is a common problem characterized by the formation of thrombus around a ruptured atherosclerotic plaque in the coronary blood vessels. 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.(1) A high degree lesion can also lead to an acute coronary syndrome (ACS) without the artery being totally occluded. Recent research has highlighted the increasingly and possibly central role of inflammation in the pathogenesis of atherosclersosis. Macrophage infiltration of plaque is key to this process.(2)

Until recently, a significant proportion of patients admitted with unstable angina progressed to myocardial infarction (MI) or died in hospital.(3,4)

Given the role of thrombin in the pathogenesis of acute coronary syndromes, heparin has the potential to decrease the occurrence of these undesirable outcomes. Although recent systematic reviews have showed a trend towards improved efficacy with the addition of unfractionated heparin (UFH) to acetylsalicylic acid (ASA) therapy,(5) these studies have failed to show a significant reduction in death and myocardial infarction. Despite this, UFH is considered the accepted treatment standard for non ST segment elevation MI

(NSTEMI) and UA(6,7) and continues to be the benchmark against which low molecular weight heparin (LMWH) and other agents are judged.

With the advent of LMWH and other agents such as glycoprotein IIb/IIIa platelet inhibitors, there is renewed interest in the role of heparins in the treatment of acute coronary syndromes. Although emerging evidence suggests that LMWH is more efficacious compared to UFH(8), there is limited data to support the role of heparins as a drug class in the treatment of ACS. This systematic review of heparins (UFH and LMWH) in the acute treatment of unstable angina and NSTEMI attempts to fill that void.

We propose to perform a focused, structured meta-analysis of any heparin compared to placebo, in the early treatment of ACS. We remain convinced that this study will represent a comprehensive review of this subject area.

2.2 Materials and Methods

Objectives: The objective of this systematic review is to determine the effect of heparins (e.g., UFH and LMWH) compared with placebo for the treatment of patients with acute coronary syndromes.

Criteria for considering studies for this review:

Types of studies: To be considered, clinical studies must be randomized controlled trials.

Types of participants: Only studies which included adult patients (> 18 years of age) presenting with ACS requiring treatment within 72 hours of presentation of their last episode of chest pain were eligible for inclusion. ACS

included UA and NSTEMI. UA had to be characterized as typical chest pain lasting at least 10 minutes with 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 appropriate cardiac enzymes (CK-MB greater than the upper normal limit or total CK greater than twice the usual upper 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 had to receive standard ASA therapy and be randomized to receive treatment with either parentral UFH or 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 and included:

- death (all cause mortality)
- myocardial infarction (MI)
- recurrent angina (anginal chest pain that required nitroglycerin infusion to be restarted)
- revascularization procedures
- major hemorrhage (fall in hemoglobin level of >20 g/L, required transfusion, was intracranial, retroperitoneal, or intraocular, or causes 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 (platelet count $<100x10^{-9}/L$)

- allergic reactions

Search strategy for identification of studies: Comprehensive searches of EMBASE (1980 to May 2002), MEDLINE (January 1966 to May 2002), CINAHL(1982 to May 2002) and the Cochrane Controlled Trials Registry (the Cochrane Library issue 4, 2002) were completed. There were no language or publication restrictions and no 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.

RETRIEVAL OF STUDIES

In Phase I, 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).

In Phase II, from the potentially relevant articles in Phase I, two reviewers (KM, BR) independently selected trials (based on the full text format) for inclusion in this review (see the appendix for inclusion criteria). Agreement was measured using simple agreement and kappa statistics. Disagreement was resolved by consensus or third party adjudication. Independent reviewers (KM, BR) abstracted 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 and the quality assessment approach was considered acceptable (kappa = 0.61). Using the Cochrane approach to assessment of allocation concealment(9), all trials were scored and entered using the following principles: Grade A: Adequate concealment; Grade B: Uncertain; Grade C: Clearly inadequate concealment. In

addition, each study was assessed using a 0-5 validated scale described previously by Jadad.(10)

DATA EXTRACTION

Data for the trials were extracted independently by two reviewers (BR, KM) and entered into the Review Manager software program. 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 vs fixed dosing, duration, target aPTT, time to adequate aPTT.

Outcome: timing of primary outcome, assessors, adjudication, definition of: MI, U/A, mortality. Side effect designation of minor and major bleeding.

Design: parallel group vs cross-over, method of randomization.

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" one.(11) In addition, quality weighting was used to test the robustness of the results

All trials were combined using the Review Manager (Update Software, Version 4.1; Oxford, UK). 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. Heterogeneity was assessed using the I^2 statistic.(12) The presence of publication bias was examined visually using a funnel plot.

Subgroups: Two specific subgroup analyses were planned *a priori*. One compared the results based on whether the subject had UA versus NSTEMI. The second compared results based on whether UFH or LMWH was used. Other sensitivity analyses were conducted on statistical testing (FE vs. RE) and methodological quality (high vs. low).

Sensitivity Analyses: In the setting of significant heterogeneity ($p < 0.1$), *a priori* we decided the groups would be divided on the following criteria:

a) Methodological quality: those studies with a Jadad score of 3 or higher vs. those with a score of less than 3.

b) Population: unstable angina vs. unstable angina and non Q-wave MI;

c) Intervention: UFH vs. LMWH.

Description of studies

The evidence for the use of heparins in acute coronary syndrome first appears in the literature in the late 1980's with studies comparing heparin versus ASA or non-ASA controls. By the mid 90's, studies began replacing UFH with

LMWH.(6,7,13-18) With the exception of two Swedish trials that enrolled nearly 1500 patients(17) and over 900 patients(7), the remaining six studies were smaller, enrolling less than 400 patients each. Two studies were conducted in Canada(6,18), one in the United Kingdom(15), one in the United States(13) and one in Argentina(16). Additionally, one study(14) was conducted in both the United Kingdom and the United States.

Designs: All studies were RCTs; however, not all were double blind. In three studies(6,17,18), concealment of allocation was adequate. In the remaining studies, there was insufficient evidence to determine whether or not there was adequate concealment. Three studies(15,16,18) reported on outcomes only over the duration of the hospital admission. In one study(17), 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.

Populations: Traditionally, heparin was started in the treatment of acute coronary syndromes based on history alone; however, in these studies patients were selected for inclusion on the basis of more narrow inclusion criteria. 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. One study(18) stipulated that patients had to present with angina within 2 weeks to 6 months following coronary angioplasty.

Interventions: The studies 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(13,14) and up to 72 hours in two other studies.(7,17) The duration of treatment varied among the different studies with a range of 2 to 7 days. ASA (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, MI, 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 vs LMWH in the treatment of ACS.(19) One study(15) reported a combined end point of death or MI and it was not possible to separate the individual event rates. 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. Of the 6 papers which included recurrent angina as a study end point, 3 required a history of typical chest pain accompanied by ECG changes.(6,13,14) The other 3 studies either did not require associated ST

segment changes to diagnose recurrent angina or were unclear how they defined this end point.(16-18) 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 3 and 2 studies respectively.

The timing of the end points was inconsistent among the trials ranging from 48 hours to 3 months. In 4 studies, endpoints were recorded over a 5 to 8 day period, while in the other 4 studies, endpoints where measured at 3 months. We have grouped the results for all reported time periods.

Methodological quality of included studies: Using the Jadad method, 4 studies representing 75% of enrolled subjects, were rated as methodologically "high quality" (6,7,17,18) and 4 were rated as "weak".(13-16) The median score was 3 with an interquartile range of 2 to 4. Using the Cochrane methodology, 4 of the 8 studies had unclear concealment of allocation.

2.3 Results

The computerized search of EMBASE, MEDLINE and CINAHL identified 2193 original publications. Independent review of the abstracts and titles of these publications identified 56 potentially relevant studies (k = 0.38). Three additional references were added from bibliographic searching of relevant articles and overviews. In total, 59 studies were reviewed for inclusion in this systematic review. Independent review of these potentially relevant articles resulted in 8

included studies, all in English, 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).(20) One potentially relevant abstract was not included as detailed methodology and outcomes could not be obtained.(21) A second study was not included(22) because it was unclear from the results to which study group the subjects had been randomized; attempts to communicate with the authors were unsuccessful. The full list of excluded studies and reasons for exclusion are listed in the Excluded Studies section.

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

Death: Death was reported as an outcome in 6 trials involving 2426 patients. Overall, there was a trend towards fewer deaths in the heparin group compared to the placebo group, but this was not statistically significant (RR = 0.84; 95% CI: 0.36, 1.98; I^2 = 0%). There was no evidence of heterogeneity (p = 0.82) in this pooled result and a fixed effects model was used when calculating the summary statistic.

Myocardial Infarction: Myocardial infarction was reported as an outcome in 6 trials involving 2426 patients. Heparins were superior to placebo in preventing MI (RR = 0.40; 95% CI: 0.25, 0.63; I^2 = 0.0%). There was no evidence of heterogeneity (p = 0.58) in this pooled result.

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, -0.04), 33 (95% CI: 25, 100) patients

would need to be treated with either type of heparin to prevent 1 additional MI in patients presenting with ACS.

Recurrent Angina: Recurrent angina was reported as an outcome in 6 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, 1.09; $I^2 = 66.6\%$).

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 showed no benefit of heparins compared to placebo in preventing revascularization procedures (RR = 0.93; 95% CI: 0.76, 1.15; $I^2 = 41.1\%$).

Multiple End Points: We were able to calculate the incidence of death or myocardial infarction for all 8 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, 0.80; $I^2 = 26.5\%$). No significant heterogeneity was identified in this result ($p = 0.22$).

The incidence of death or MI 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,-0.05), 33 (95% CI: 20,100) patients would need to be treated with heparin to prevent 1 additional death or MI.

Major Bleeds: Eight trials, involving 3118 patients, reported major bleeds as an outcome. There was a trend towards more major bleeds in the heparin group compared to control group; however, this did not reach the required level of statistical significance (RR = 2.05; 95% CI: 0.91, 4.60; I^2 = 0.0%). No heterogeneity was observed in this outcome (p = 0.93).

Minor Bleeds: Only 3 of the 8 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, 37.49; I^2 = 66.9%). In the heparin group, 8.0% (79/989) pf 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, 0.11), such that for every 17 (95% CI: 9,50) patients treated with heparin, 1 additional case of minor bleeding was observed.

Thrombocytopenia: Only 2 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 control in the occurrence of thrombocytopenia (RR = 0.20; 95% CI: 0.01, 4.24; I^2 = 0.0%).

SENSITIVITY ANALYSES

Sensitivity analyses based on a RE versus FE modelling yielded very similar results. With the exception of recurrent angina, the pooled statistic for all other outcomes was essentially unchanged regardless of whether a RE or FE model was chosen. If a FE instead of a RE model had been used for recurrent

angina, the point estimate would have remained essentially unchanged, however, the 95% confidence interval would have been narrowed making the reduced incidence of recurrent angina in the heparin treated group statistically significant (RR = 0.79; 95% CI: 0.67, 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 ANAYLSES

Subgroup analysis based on whether patients had UA versus a NSTEMI were 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 8 included studies, only 2(16,17) 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(23) propose the I^2 statistic which describes the percentage of total variation across studies that is 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 was analyzed according to the treatment received, clinically important subgroups were identified. The pooled analysis from the LMWH sub-group showed statistically significant benefit

with respect to the incidence of recurrent angina (p = 0.52; 95% CI: 0.36, 0.74) and revascularization procedures (p = 0.26; 95% CI: 0.09, 0.78), even though this benefit was lost when all heparins were grouped together.

2.4 Discussion

This systematic review examines the best available evidence for the use of heparins in the treatment of ACS and identifies 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 (~1-2%), this SR 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 MI such that 33 patients needed to be treated with heparin to prevent 1 additional MI.

Half of all eligible subjects 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 MI, 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 (1-3%) 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 seen 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. Heparins appeared to be a safe treatment for ACS. 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 2 studies commented on this rare but potentially life-threatening complication of heparinization. These data must be interpreted with caution, however, as side-effects were poorly reported in most studies.

There is a possibility of publication bias in this systematic review. For example, by missing unpublished 'statistically' negative trials we may be over-estimating the effect of heparin treatment. However, a comprehensive search of the published literature for potentially relevant studies was conducted, using a systematic strategy to avoid bias. This was followed by attempts to contact

corresponding and first authors. Although no unpublished or negative trials were identified, we recognize that these types of trials may exist. The funnel plot demonstrates asymmetry in the area of small negative trials, so this is a legitimate concern. Given the nature of the research (e.g., expensive, complex, difficult to fund), however, these small negative trials are unlikely, and would not be expected to influence the results. There is also a possibility of study selection bias. Five trials in which the study group did not receive ASA or were compared versus a non-ASA control were excluded(24-28) because of the well-accepted treatment of ACS with ASA.(6,5,29) 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.

This systematic review illustrates the potential benefit of using heparins in the early of treatment of ACS. Patients presenting with UA or NSTEMI should be considered for a 5 to 8 day course of heparin 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 heparins for acute coronary syndrome. Therefore, we cannot recommend the indiscriminate use of heparins in ACS. UFH or LMWH must be reserved for those patients with either NSTEMI or high-risk UA as defined above. Furthermore, 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.

These results are concordant with the most current recommendations made by the American Heart Association(30,31) and similar to two previous reviews.(5,32) The AHA suggests using either LMWH or UFH for patients with intermediate to high risk UA or NSTEMI. Although in our sub-group analysis, only LMWH appeared to be statistically superior to ASA alone, there was a relatively small reduction in the absolute risk.

CONCLUSIONS

Implications for practice

This systematic review of randomized controlled trials supports the use of heparins in the early treatment of ACS. Given in addition to ASA 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 MI, but not mortality. In this review, heparins were given within 24 to 72 hours of the onset of symptoms as a weight-adjusted dose for a 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 MI, recurrent angina and the need for revascularization procedures. Given the advantages of LMWH over UFH demonstrated in a previous review(19) and the evidence reported here, LMWH should be the agent of choice in the early

treatment of UA 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.(33)

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) would affect outcomes.
- 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.
- 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.

Potential conflict 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, Dr. Magee and Dr. Rowe have received speakers fees from several makers of LMWH (e.g., Pfizor, Aventis, Sanofi) for educational purposes, but none of the staff are paid consultants or shareholders of any pharmaceutical company that produces LMWH.

Table 2.1: Study populations

Study	Location	Year	Total Sample	Incidence of MI (%)	Incidence of Death (%)
Theroux(6)	Canada	1988	479*	4.4	0.4
Cohen 1990 (12)	United States	1990	93**	4.3	1.1
RISC(7)	Sweden	1990	945***	6.3	0.3
Cohen 1994 (13)	United States, United Kingdom	1994	214	7.0	1.9
Holdright(14)	United Kingdom	1994	285	unable to calculate	unable to calculate
Gurfinkel(15)	Argentina	1995	219	5.2	0.0
FRISC(16)	Sweden	1996	1506	2.9	1.0
Doucet(17)	Canada	2000	200	0.0	0.0

*243 patients eligible for inclusion in meta-analysis
**69 patients eligible for inclusion in meta-analysis
***399 patients eligible for inclusion in meta-analysis

Table 2.2: Study design

Study	Type of heparin	Initiation of therapy	Duration of heparin therapy	Timing of Outcomes	Overall Conclusion	Cochrane Score	Jadad Quality Score
Theroux (6)	UFH	within 24 hrs	6 days	6 days and 3 months	UFH more effective	A	4
Cohen 1990(12)	UFH	within 48 hrs	3-4 days	12 weeks	UFH more effective	B	1
RISC(7)	UFH	within 72 hrs	5 days	5, 30 and 90 days	no difference	B	3
Cohen 1994(13)	UFH	within 48 hrs	3-4 days	12 weeks	UFH more effective	B	2
Holdright (14)	UFH	within 24 hrs	2 days	duration of hospital admission	no difference	B	2
Gurfinkel (15)	UFH and nadroparin	within 24 hrs	5-7 days	5 to 7 days	LMWH more effective	B	2
FRISC(16)	UFH and dalteparin	within 72 hrs	6 days	6, 40 and 150 days*	LMWH more effective	A	3
Doucet (17)	UFH	within 24 hrs	2-4 days	58 to 96 hours	no difference	A	4

*Used in-patient data for meta-analysis

Figure 2.1: Comparison of any heparin with ASA to controls with ASA only and its effect on mortality.

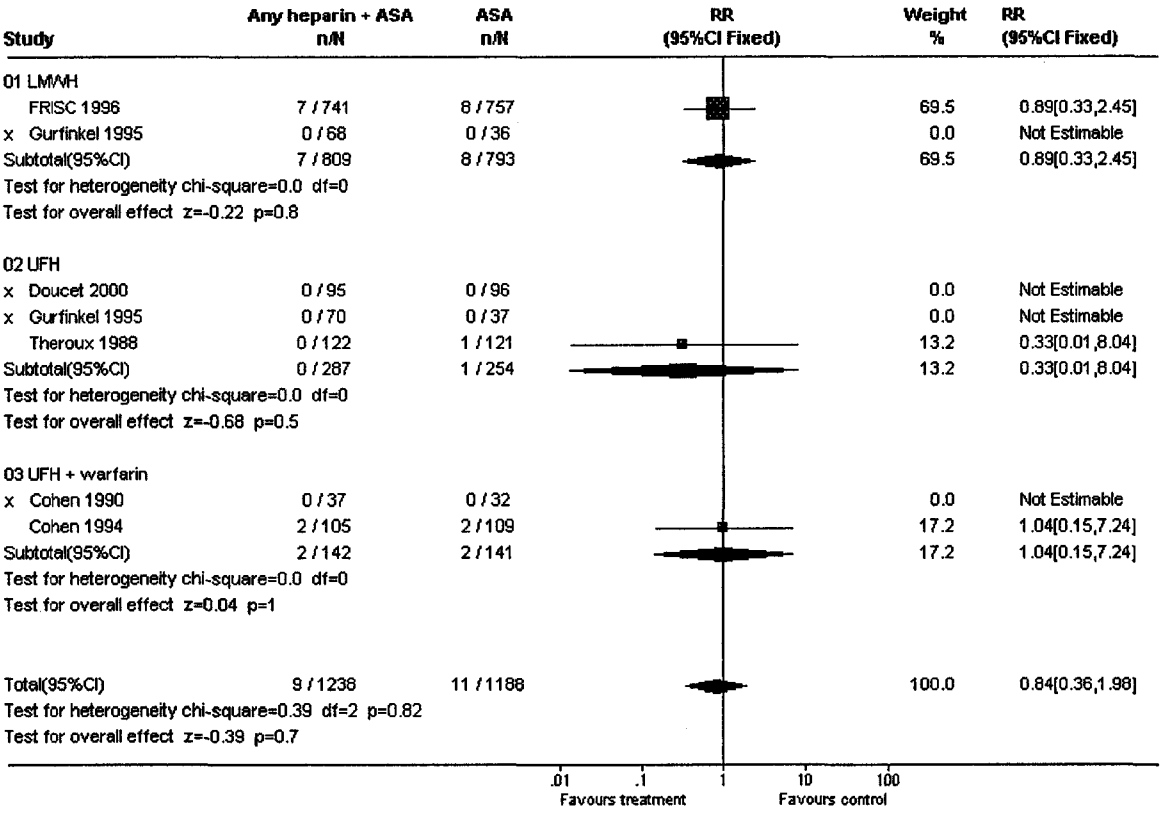


Figure 2.2: Comparison of any heparin with ASA to controls with ASA only and its effect on MI.

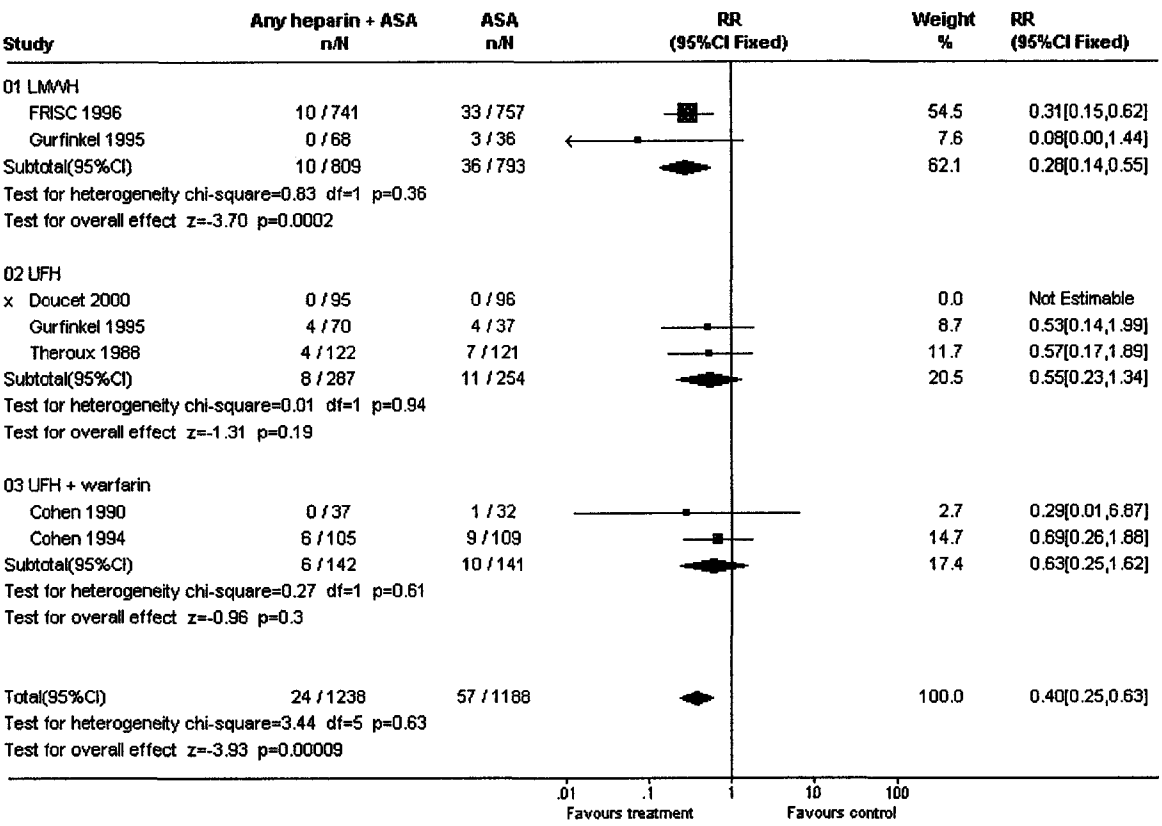


Figure 2.3: Comparison of any heparin with ASA to controls with ASA only and its effect on recurrent angina.

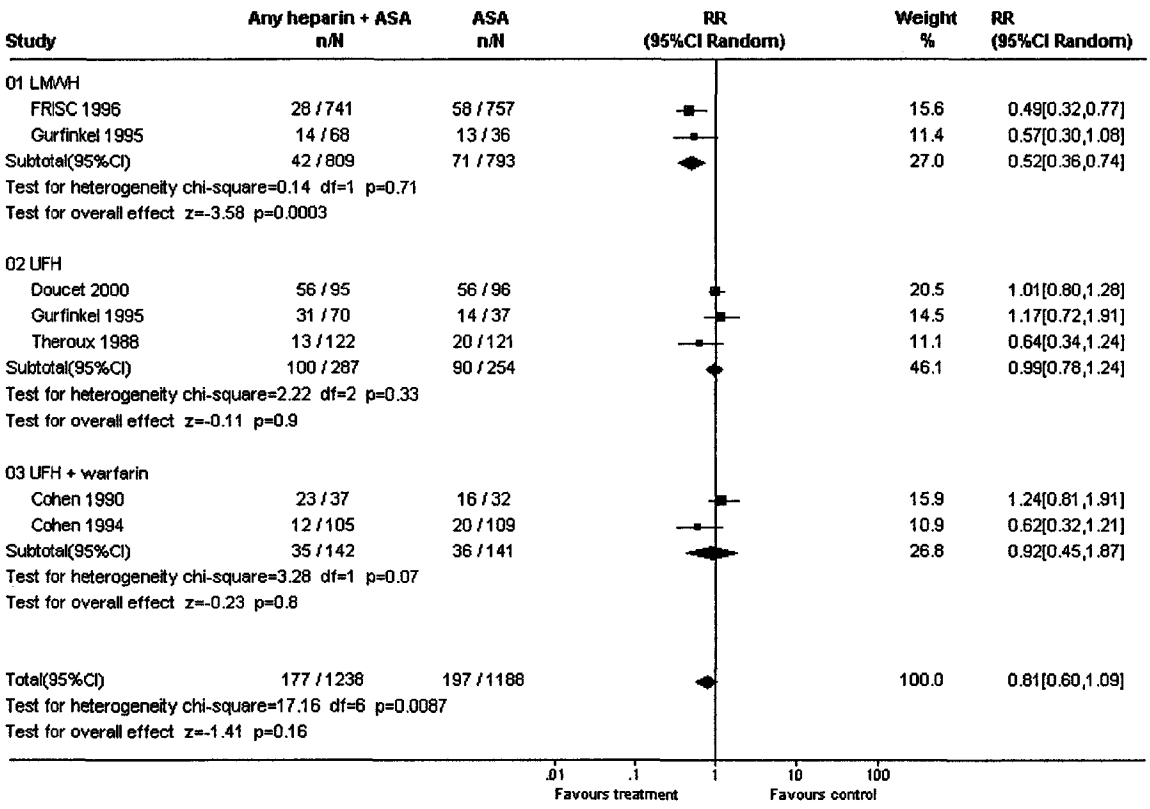


Figure 2.4: Comparison of any heparin with ASA to controls with ASA only and its effect on revascularization procedures.

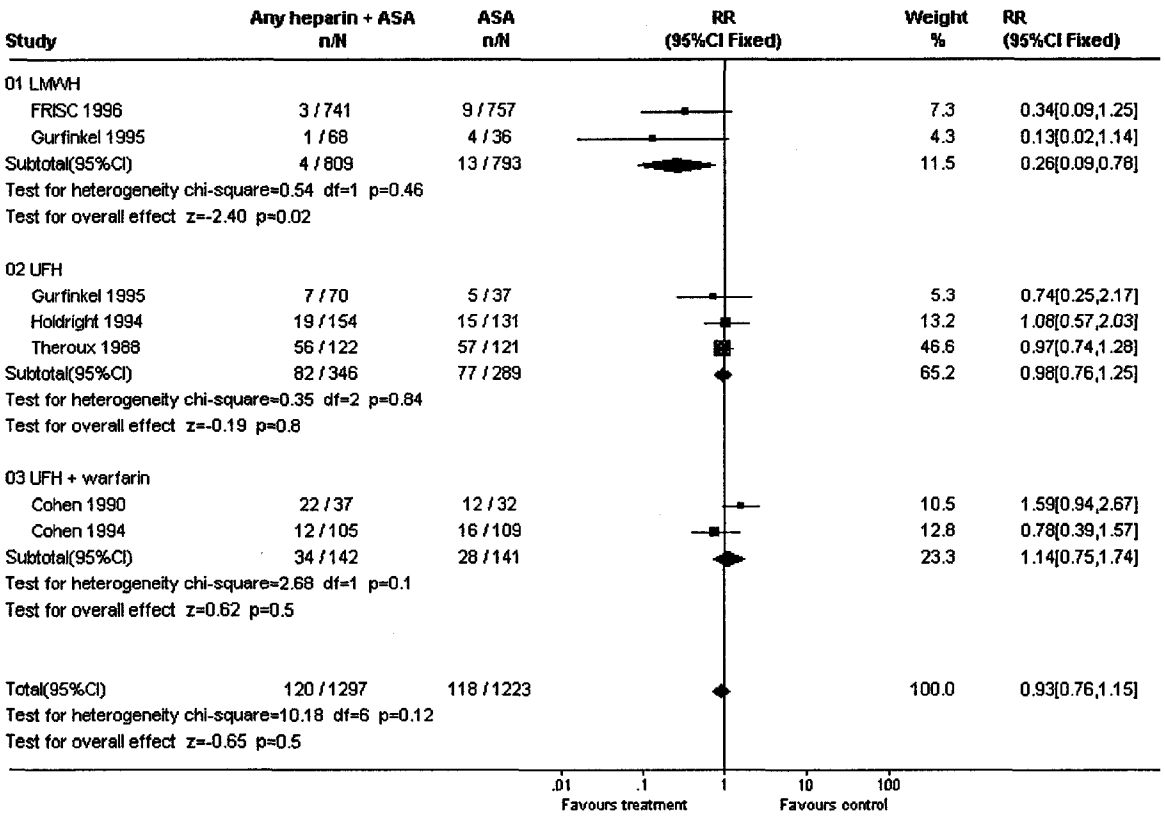


Figure 2.5: Comparison of any heparin with ASA to controls with ASA only and its effect on multiple end points (death or MI).

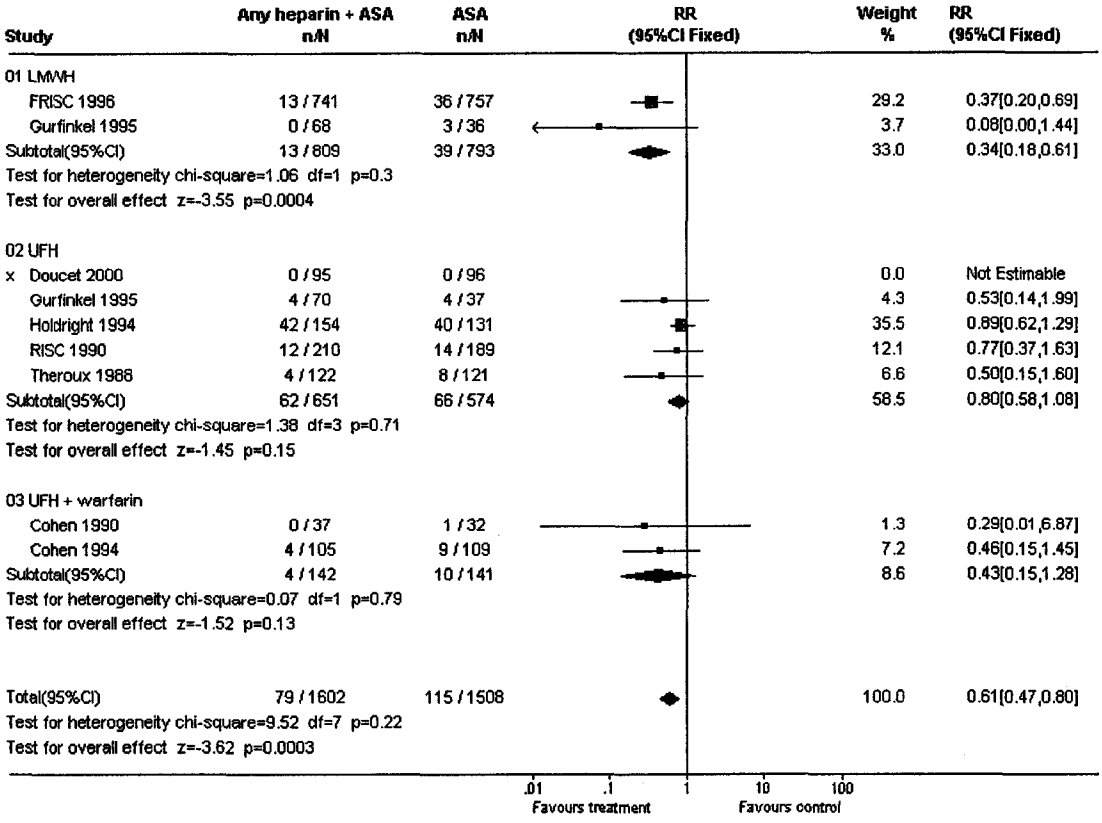


Figure 2.6: Comparison of any heparin with ASA to controls with ASA only and its effect on major bleeds.

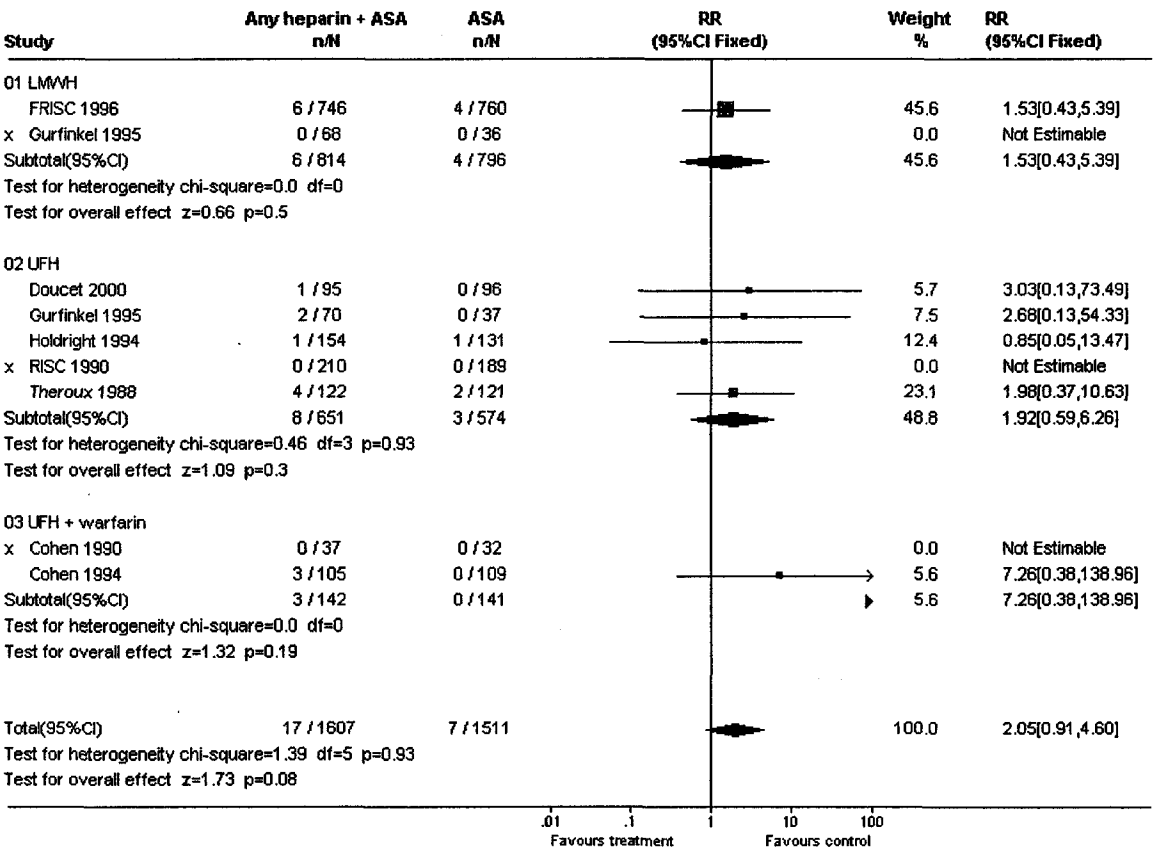


Figure 2.7: Comparison of any heparin with ASA to controls with ASA only and its effect on minor bleeds.

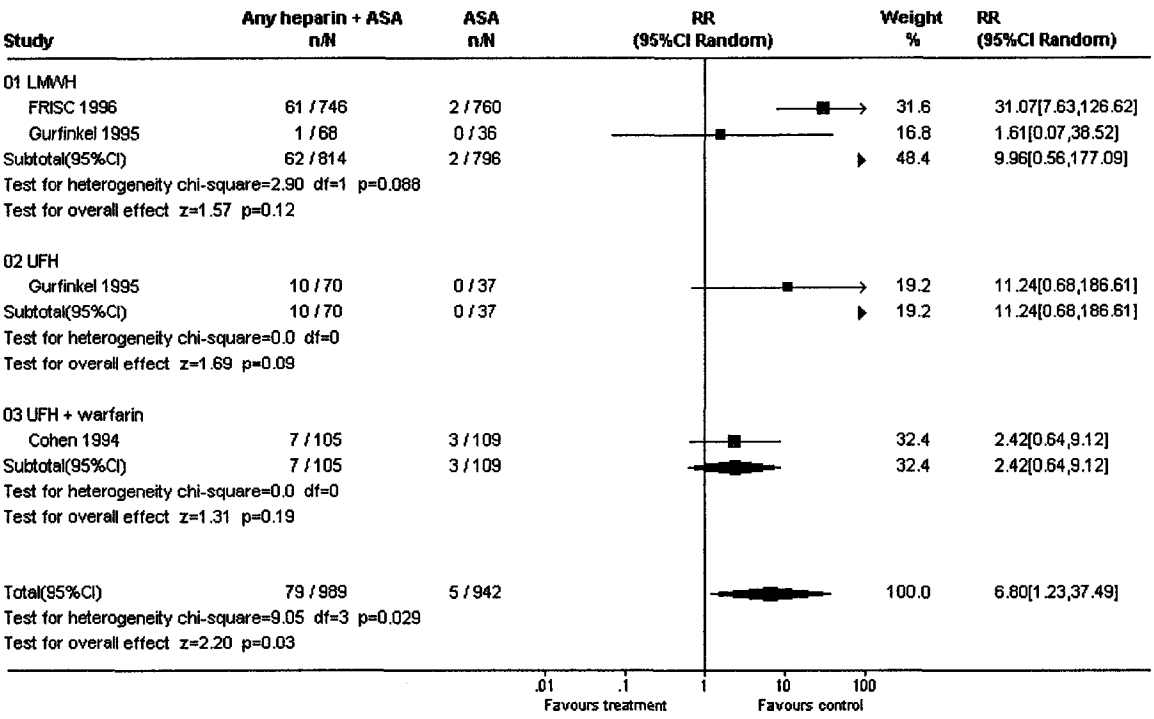
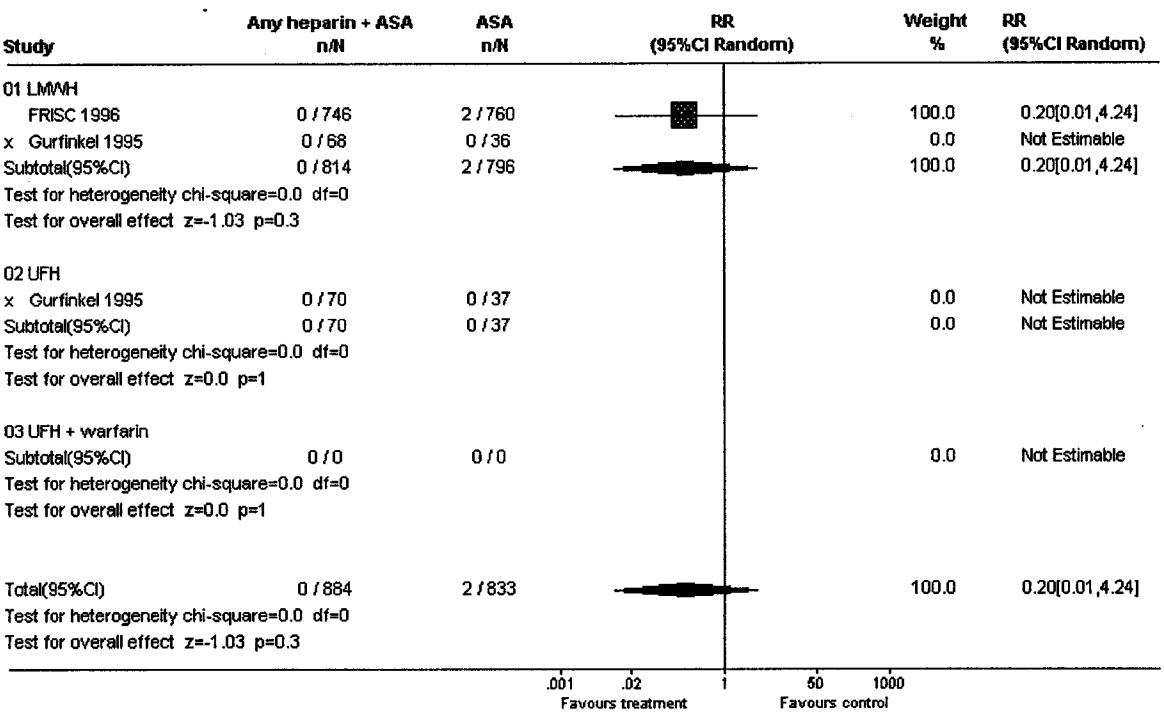


Figure 2.8: Comparison of any heparin with ASA to controls with ASA only and its effect on thrombocytopenia.



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Chapter Three

Low molecular weight heparins versus unfractionated heparins for acute coronary syndromes

3.1 Introduction

Unstable angina (UA) 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.(1) 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 UA progressed to (MI) or died in hospital.(2)

The diagnosis of UA and non-ST segment elevation MI (NSTEMI) (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 (ACS). NSTEMI is differentiated from UA by presence of elevated cardiac enzyme markers (creatine kinase or troponin) detected in the blood. Management of ACS is similar for both disorders and has advanced dramatically in the last decade. Current treatment includes acetylsalicylic acid (ASA), oxygen, cardiac monitoring, bed rest and other therapeutic and procedural interventions.

Despite weak evidence, the use of unfractionated heparin (UFH) in ACS is now considered an accepted treatment standard for NSTEMI and UA.(3,4) Unfortunately, there are many logistical problems (e.g., need for therapeutic monitoring, regular adjustments in treatment, etc.) and side effects (e.g., minor and major bleeding) associated with its use. Even with ASA treatment in combination with UFH, there is still a 20% failure rate (death, MI or recurrent angina) at three months.(5) As well, agreement on the diagnosis of UA 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.(6) 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.(7) LMWH lack some of the shortcomings of UFH in that they have a predictable anticoagulation effect, fewer bleeding complications, and a lower incidence of HIT.(8) Traditionally, LMWH have been considered to be equivalent to UFH in ACS 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.(9-11)

Currently, there is considerable interest in the use of LMWH in the treatment of ACS given its ease of use, cost efficiency, and more favourable therapeutic profile compared to UFH. Indeed, enoxaparin has already been approved in the United States for use in UA and NSTEMI. 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 ACS,(12,13) they have, through their methodological limitations, lacked the power of a formal systematic review. This systematic review of LMWH in the acute treatment of ACS 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.

3.2 Materials and Methods

Objectives: To compare the effects (harms and benefits) of LMWH with UFH for the treatment of patients with ACS with respect to death, MI, recurrent angina and side effects.

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 ACS requiring treatment within 72 hours of

presentation were eligible. For this review, we defined acute coronary syndrome to include UA and NSTEMI. UA was defined as typical chest pain lasting at least 10 minutes within 72 hours of presentation with historic, electrocardiographic or angiographic evidence of underlying ischemic heart disease. NSTEMI 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 intervention: 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 and included:

- death;
- MI;
- recurrent angina (anginal chest pain that requires nitroglycerin infusion to be restarted);
- revascularization procedures (e.g., angioplasty, stenting, bypass grafting);
- 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 $<100 \times 10^{-9}/L$);
- 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.

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 ACS was made to identify other potentially relevant studies.

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, BR). 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 (κ) statistics. Disagreement was resolved by consensus or third party adjudication. Independent reviewers (KM, BR) abstracted 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. Using the Cochrane approach to assessment of allocation concealment (14), all trials were scored using the following principals:

Grade A: Adequate concealment;

Grade B: Uncertain;

Grade C: Clearly inadequate concealment.

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(15) 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; Update Software, Oxford, UK).

STATISTICAL CONSIDERATIONS

An analysis was completed which deals with the "missing data" issues from the individual trials. Data from all trials were combined using the Meta

analysis software in Review Manager (Version 4.1). 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 statistically significant 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 RE model.

Specific subgroups were planned *a priori*. First, to compare UA to NSTEMI and second, to compare results based on the specific LMWH used. Other planned sensitivity analyses were: mixed vs. random effects and methodological quality (high vs. low). If significant heterogeneity ($p < 0.1$) existed, the groups were to be divided on the following order:

a) Methodological quality: Jadad score of 3 or greater vs. Jadad score of less than 3;

b) Population: UA vs. UA and NSTEMI;

c) Intervention: different types of LMWH.

Description of studies

The evidence for the use of LMWH in ACS is recent, appearing in the published literature within the last 5 years.(16-22) 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 ACS based on history alone. In the presently reviewed studies, patients were selected for inclusion on the basis of a stricter 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 11,128 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(17) and 72 hours in another.(18) The duration of therapy varied among the studies with the majority of patients receiving treatment for 5 to 8 days. ASA (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, 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. MI 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(16,18,22) 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), sub-acute (3-14 days), and late (greater than 14 days).

Methodological quality of 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"(16,17,22) and 4 were rated as "weak".(18-21) 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.

3.3 Results

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 Spanish), with a total of 11128 patients being included in this systematic review (κ = 1.0). Two potentially relevant abstracts were not included as detailed methodologies and outcomes could not be obtained.(23,24) One recently published study(25) 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 (11,128 participants) showed some evidence of heterogeneity (p = 0.10) 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 = 1.02; 95% CI: 0.70, 1.47).

Myocardial infarction: LMWH were superior to UFH in preventing MI (RR = 0.81; 95% CI: 0.68, 0.97) when data were pooled from all time periods following onset of treatment (n=11,128). There was no heterogeneity in this pooled analysis (p = 0.30) of data from 7 trials. LMWH were superior to UFH in preventing MI (RR = 0.80; 95% CI: 0.66, 0.96) 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 4.0% (218/5595) for patients treated with LMWH, and 4.8% (266/5533) for those treated with UFH. Given the risk difference of 0.008, 125 patients would require treatment with LMWH to prevent 1 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 (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.(16,17)

Revascularization procedures: Seven trials reported revascularization procedures within 2 weeks of admission to the 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 1 additional revascularization procedure.

Multiple end points: When a combined event or multiple end point was recorded in the trials, it consisted of the numbers of deaths, MI, recurrent angina and revascularizations. LMWH were superior to UFH (RR = 0.80; 95% CI: 0.67, 0.95) for prevention of combined endpoints during the early phase, up to 48 hours after treatment (n=7081). LMWH were superior to UFH (RR = 0.80; 95% CI: 0.66, 0.98) for prevention of combined endpoints during the sub-acute period and 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 1 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 sensitivity analysis based on trial quality assessment eliminated 4 papers (18-21); the outcomes were unchanged based on this quality comparison.

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.

3.4 Discussion

This systematic review examined the best available evidence for the use of LMWH in the emergency management of ACS. 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. Given the relatively low incidence of death in the included studies, this SR was under-powered to detect small differences in treatment effects. For this outcome, the systematic review had 80% power to detect a relative reduction in risk of 36% (from 1.79% to 1.15%). Approximately 19000 patients in each group would have been required to detect at 20% reduction in risk (power = 80%, two-sided alpha = 0.05). However, treatment with LMWH 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 ACS. Patients presenting with UA or NSTEMI 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 NSTEMI or high-risk UA as defined above. Furthermore, in those centres with active primary cardiac catheterization facilities, 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.(26)

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 1 additional MI. This is similar to the difference between tPA and streptokinase commonly quoted in the ST segment elevation MI literature.(27)

In terms of safety, LMWH appears to be superior to UFH. While a previous systematic review demonstrated less major bleeding when LMWH was

compared to UFH in VTE (28), 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 (12), 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".(29) 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(13) concluded "there is no convincing difference in efficacy or safety between LMWH and UFH." The Eikelboom systematic review did not include two trials(20,21) included in this study. Yet, their review still included the large bulk of patients (nearly 11,000 of the 11,128), 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 (AHA).(30,31) The AHA suggests using either LMWH or UFH for patients with intermediate to high risk UA or NSTEMI. Although LMWH appeared to be statistically superior to UFH, there was a relatively small reduction in absolute risk. The AHA recommends using both heparin and IIb/IIIa glycoprotein inhibitors for high-risk patients. As the safety of combining LMWH and glycoprotein IIb/IIIa inhibitors has not yet been established, the use of LMWH in this situation awaits further investigation.

REVIEWER'S CONCLUSIONS

Implications for practice

This systematic review of randomized controlled trials supports the use of subcutaneous LMWH in the early treatment of ACS. 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 directly 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.
- 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.

Potential Conflict 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, Dr. Magee and Dr. Rowe have received speakers fees from several makers of LMWH (e.g., Pfizor, Aventis, Sanofi) for educational purposes, but none of the staff are paid consultants nor shareholders of any pharmaceutical company that produces LMWH.

Table 3.1: Study Population

Study	Location	Year	Total Sample	Incidence of MI (%)	Incidence of Death (%)
ESSENCE(16)	North America, South America, Europe	1997	3171	4.5	3.3
FRAXIS(17)	South America, Europe, Asia,	1999	2317	5.8	3.9
FRIC(18)	North America, Europe	1997	1482	2.8	0.9
Godoy(19)	South America	1998	70	1.4	0
Gurfinkel(20)	South America	1995	138	2.9	0
Suvarna(21)	Asia	1997	40	0	0
TIMI 11B(22)	North America, South America, Europe	1999	3910	4.1	1.9

Table 3.2: Study design

Study	Type of LMWH	Initiation of LMWH	LWMH Regime	Timing of Outcomes	Overall Conclusion	Cochrane Score	Jadad Quality Score
ESSENCE (16)	Enoxaparin	within 24 hrs	100 anti-factor Xa units/kg sc bid for 48 hrs to 8 days	48hrs, 14 days and 30 days	LMWH more effective	B	4
FRAXIS (17)	Nadroparin	within 48 hrs	86 AXa IU/kg iv then Group I: 86 AXa IU/kg sc bid for 6 days or Group II: for 14 days	6 days, 14 days, 3 months	No difference	B	4
FRIC(18)	Dalteparin	within 72 hrs	120 IU/kg sc bid for ~6 days	6 days	No difference	B	2
Godoy (19)	Nadroparin	within 24 hrs	0.6 ml sc bid for 3 to 5 days	3 to 5 days	LMWH more effective	C	2
Gurfinkel (20)	Nadroparin	within 24 hrs	214 Axa IU/kg sc bid for 5 to 7 days	5 to 7 days	LMWH more effective	B	2
Suvarna (21)	Tinzaparin	within 24 hrs	3500 units sc bid for 5 days	5 days	No difference	C	1
TIMI 11B (22)	Enoxaparin	within 24 hrs	30 mg iv the 1 mg/kg sc bid for ~8 days	8 days	LMWH more effective	B	3

Figure 3.1: Comparison of LMWH to controls with UFH and its effect on early death (< 48 hours).

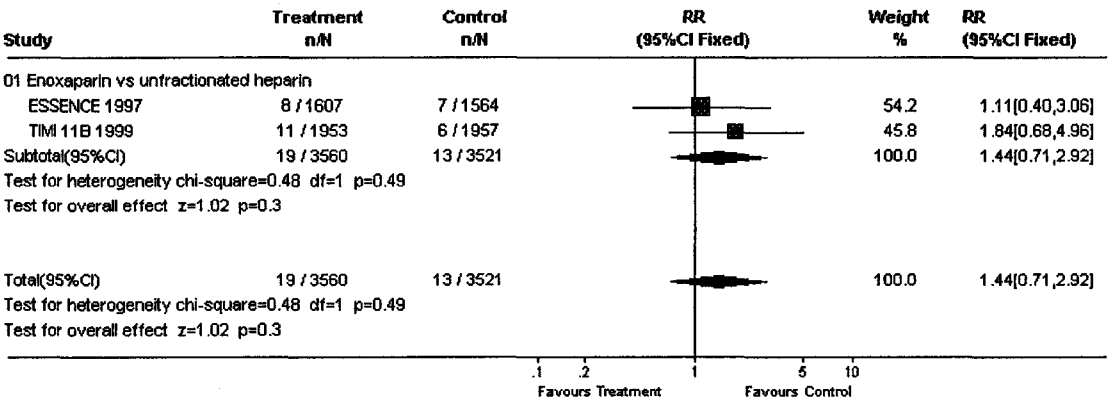


Figure 3.2: Comparison of LMWH to controls with UFH and its effect on death in the sub-acute phase (3-14 days).

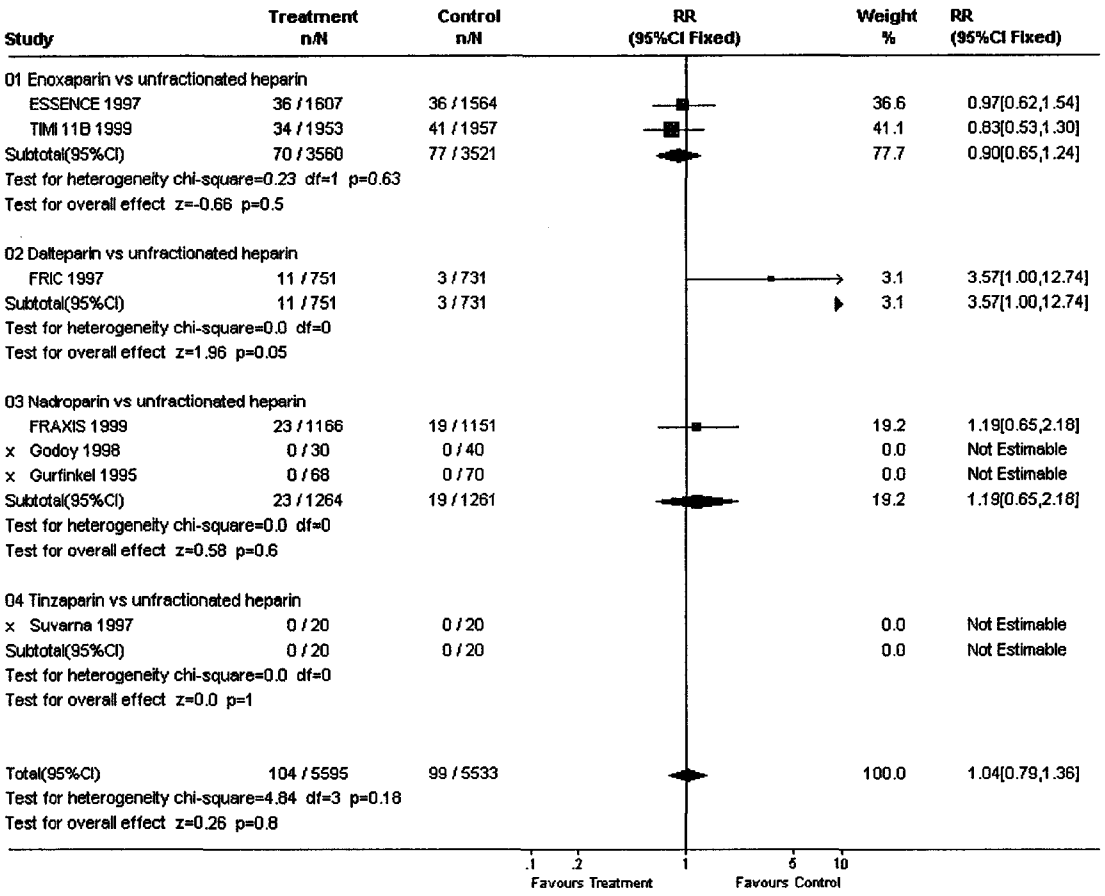


Figure 3.3: Comparison of LMWH to controls with UFH and its effect on late deaths (> or = 30days).

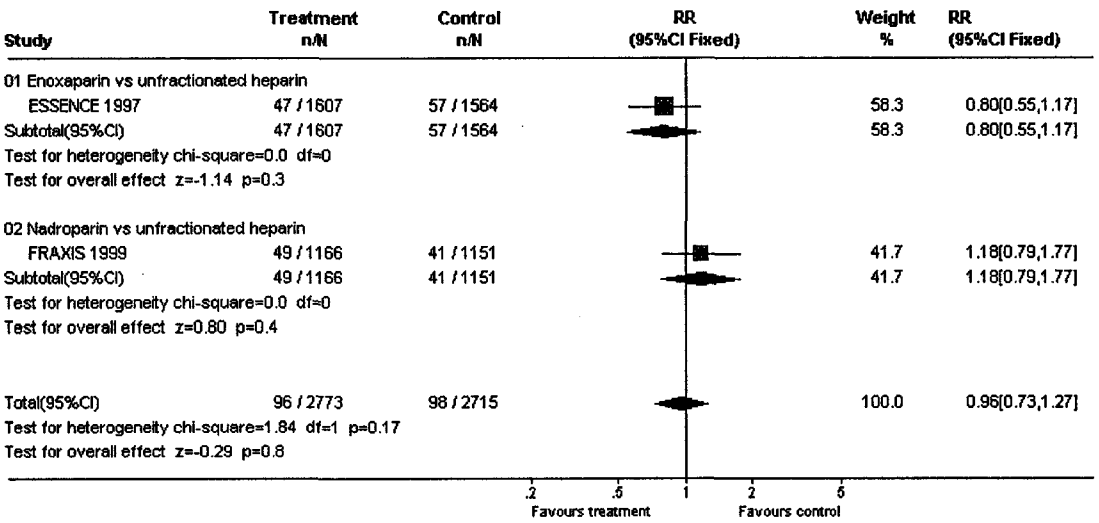


Figure 3.4: Comparison of LMWH to controls with UFH and its effect on death over all time periods.

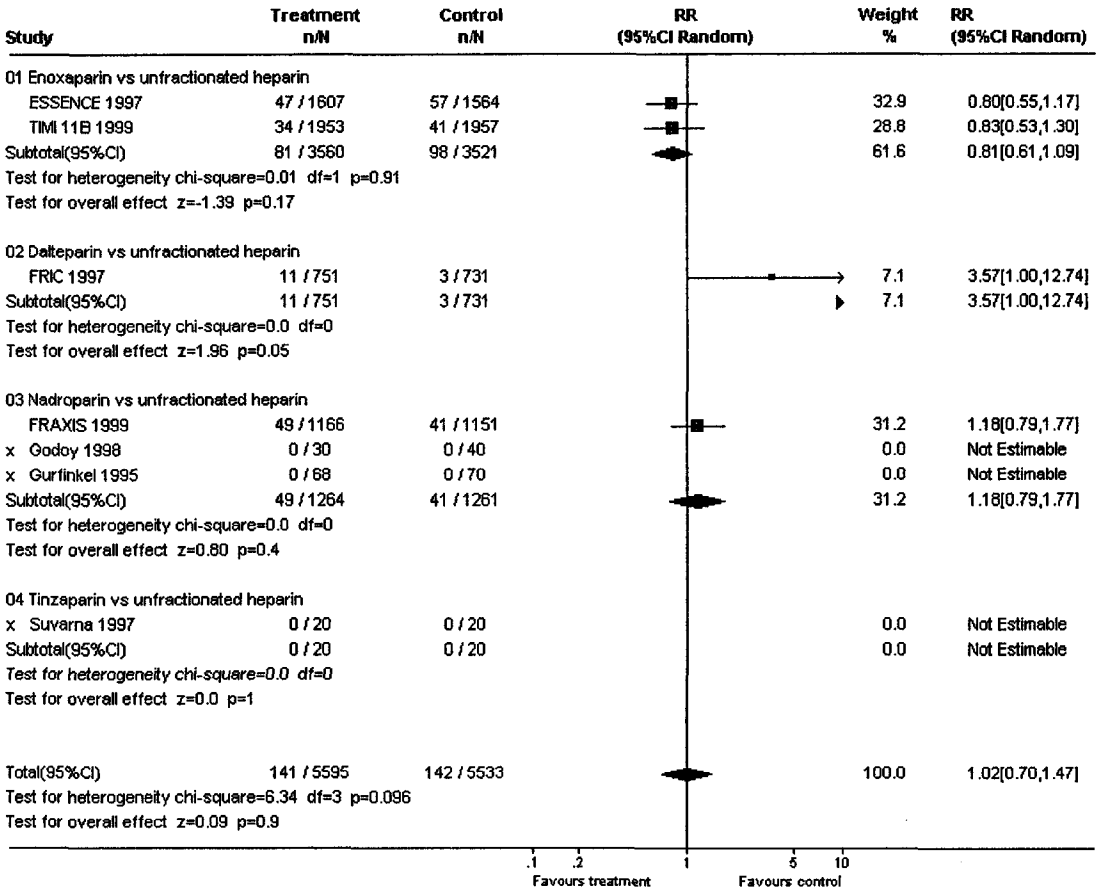


Figure 3.5: Comparison of LMWH to controls with UFH and its effect on early MI (< 48 hours).

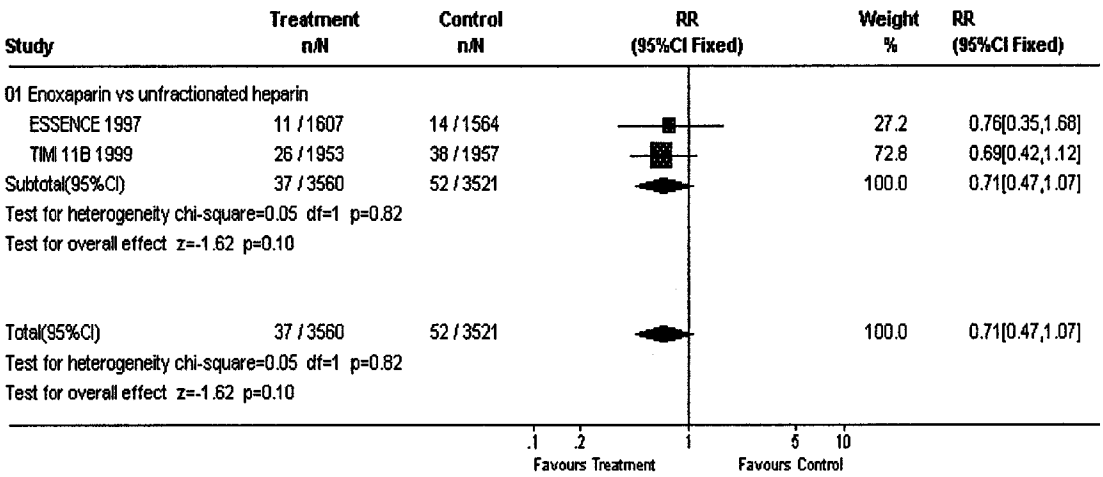


Figure 3.6: Comparison of LMWH to controls with UFH and its effect on MI in sub-acute period (3-14 days).

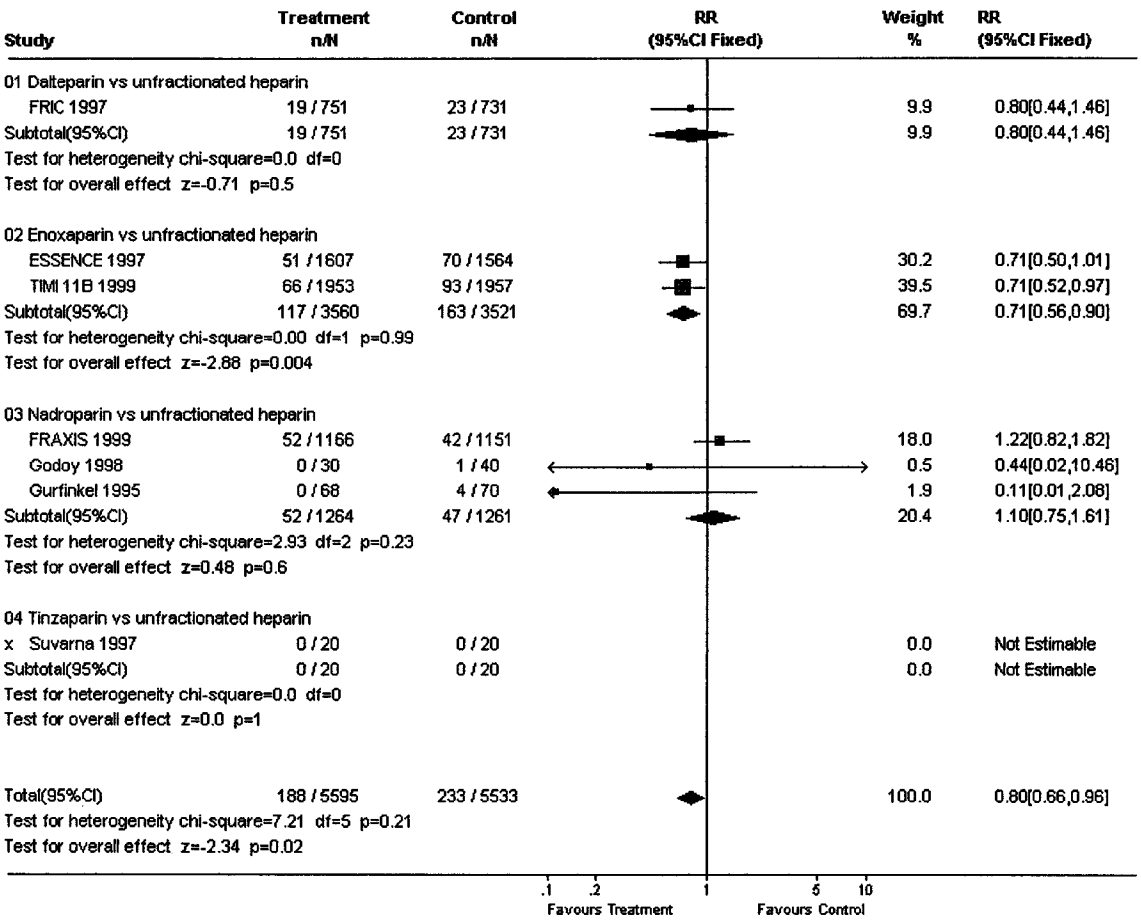


Figure 3.7: Comparison of LMWH to controls with UFH and its effect on late MI (> or = 30 days)

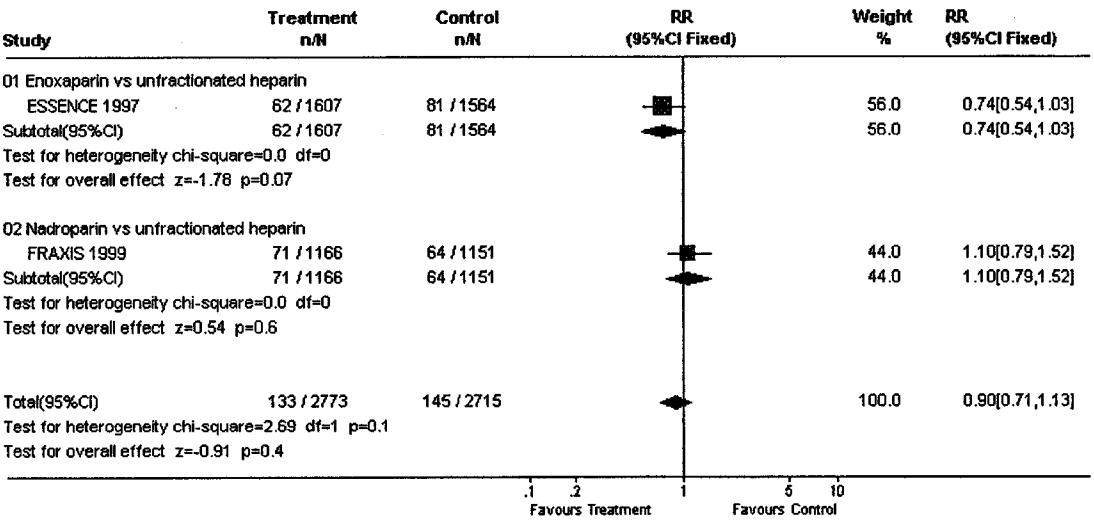


Figure 3.8: Comparison of LMWH to controls with UFH and its effect on MI over all periods.

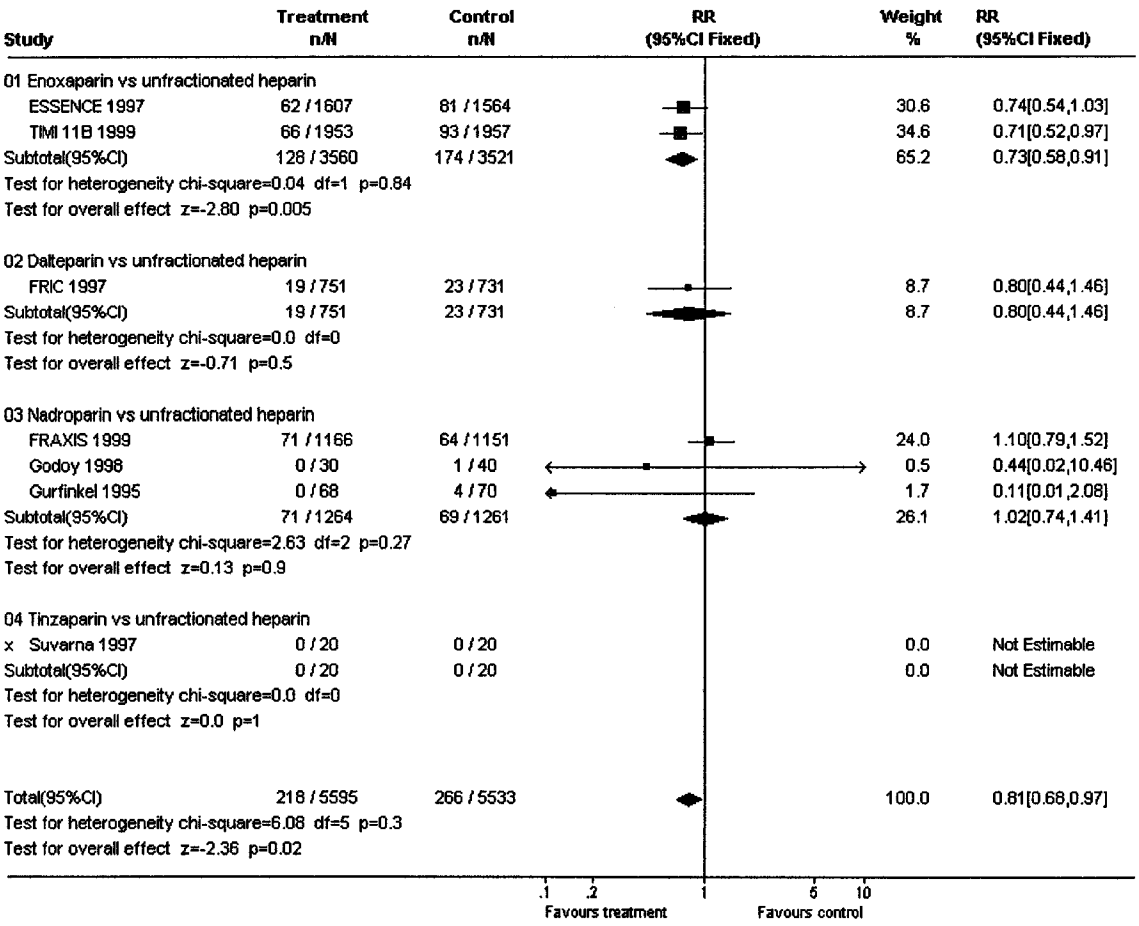


Figure 3.9: Comparison of LMWH to controls with UFH and its effect on early recurrent angina (48 hours).

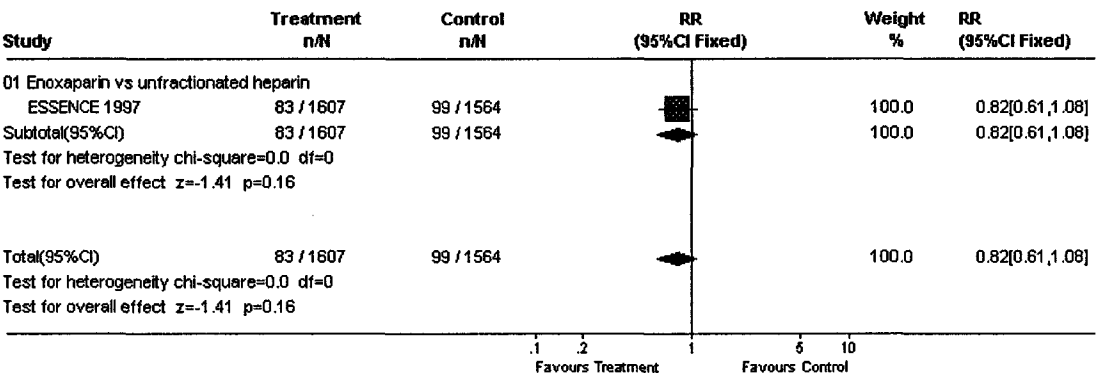


Figure 3.10: Comparison of LMWH to controls with UFH and its effect on recurrent angina in the subacute period (3-14 days).

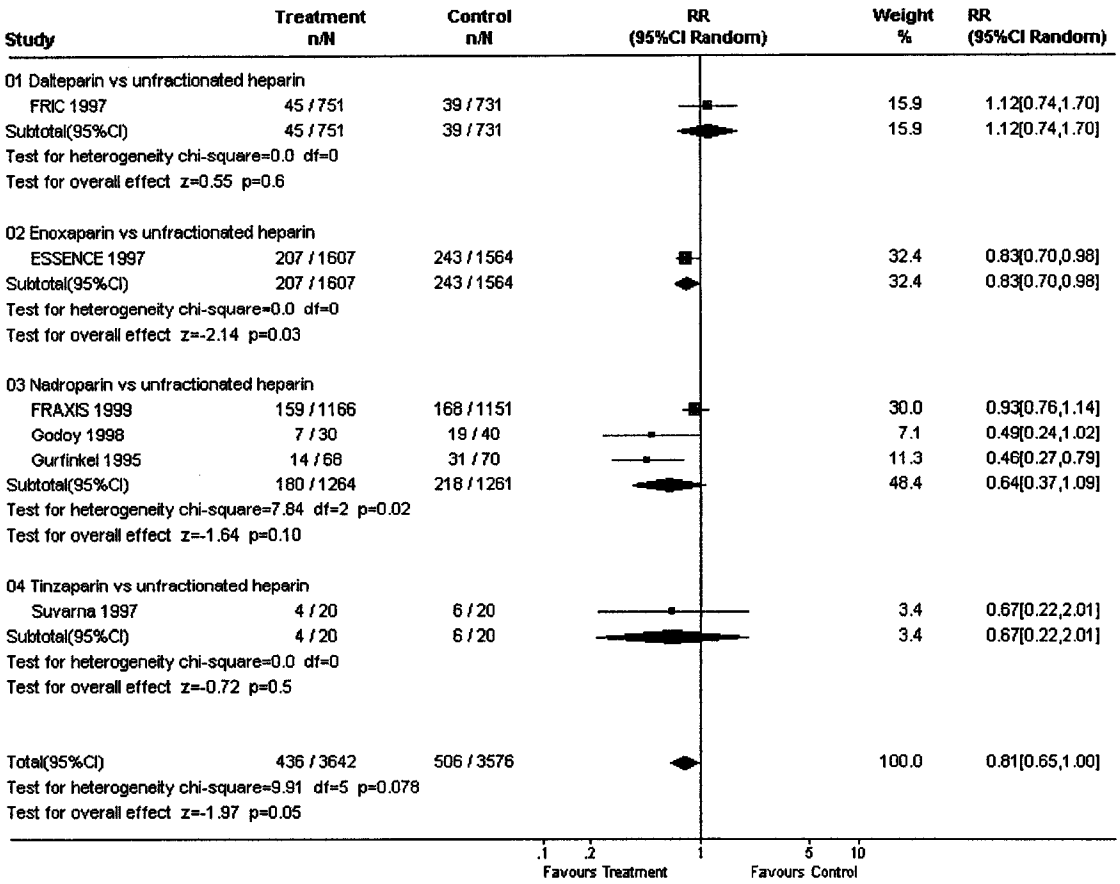


Figure 3.11: Comparison of LMWH to controls with UFH and its effect on late angina (> or = 30 days).

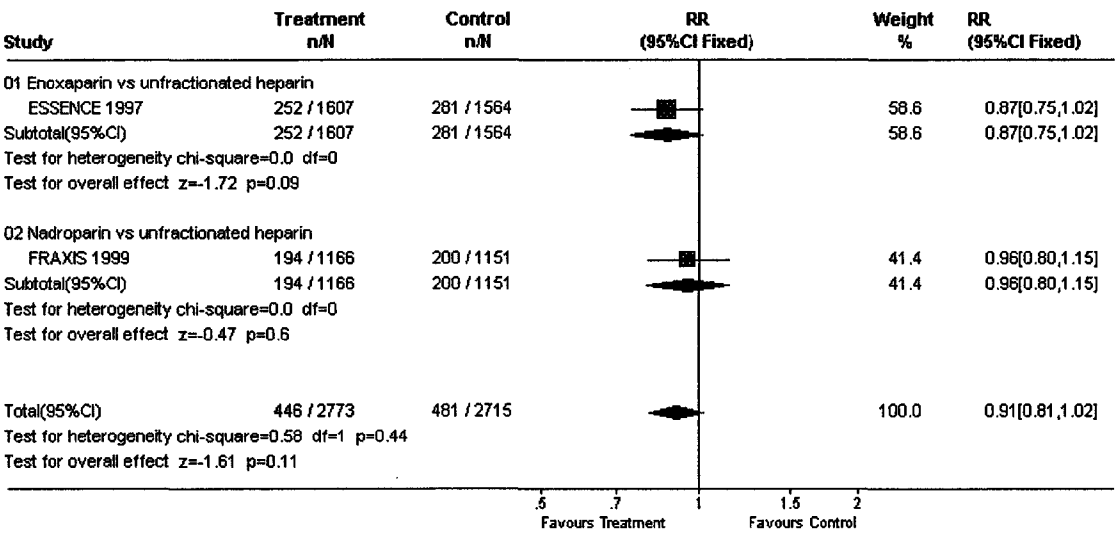


Figure 3.12: Comparison of LMWH to controls with UFH and its effect on recurrent angina over all time periods.

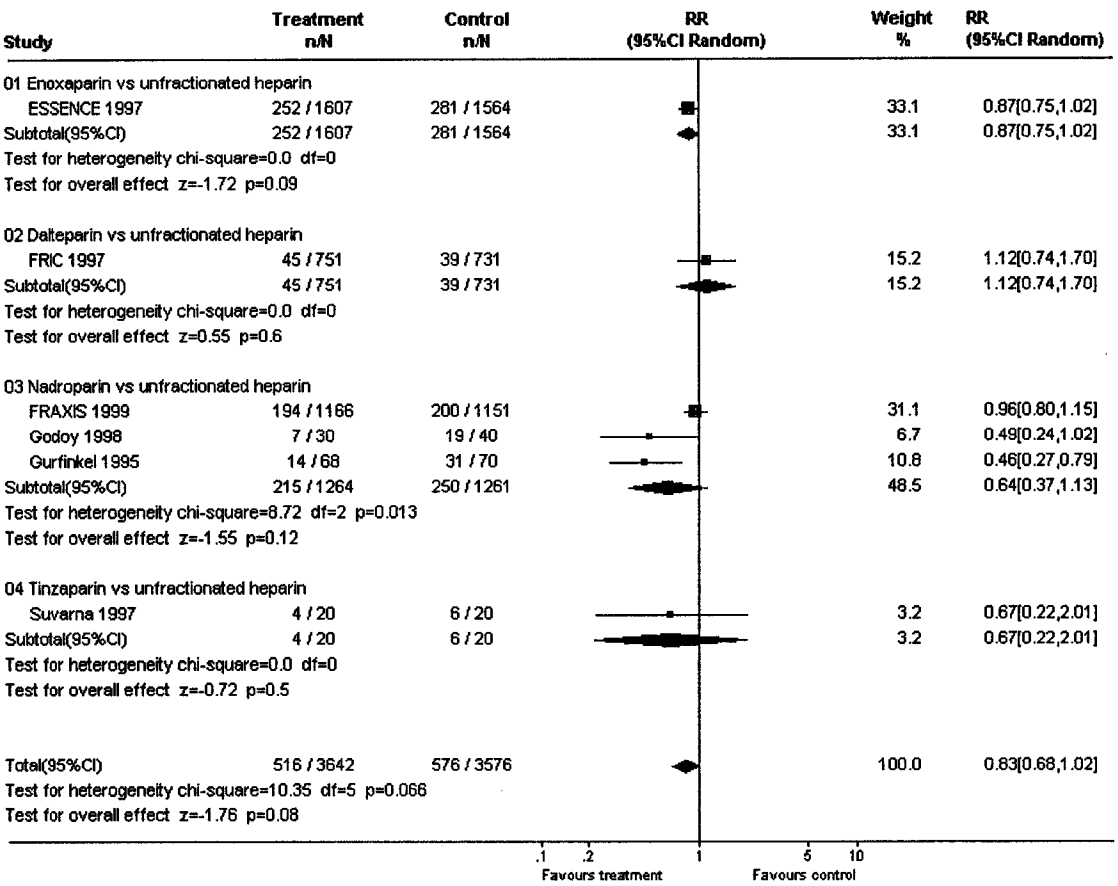


Figure 3.13: Comparison of LMWH to controls with UFH and its effect on revascularization.

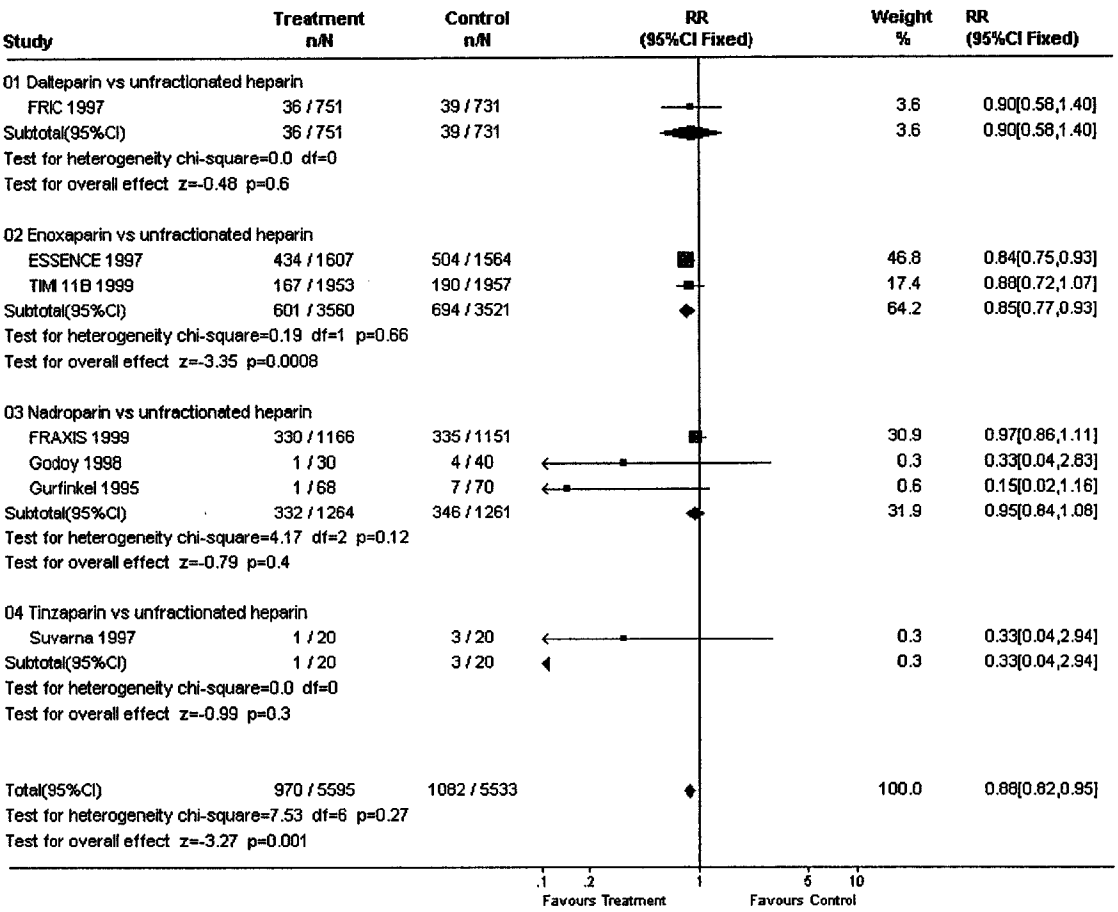


Figure 3.14: Comparison of LMWH to controls with UFH and its effect on multiple end points (< 48 hours).

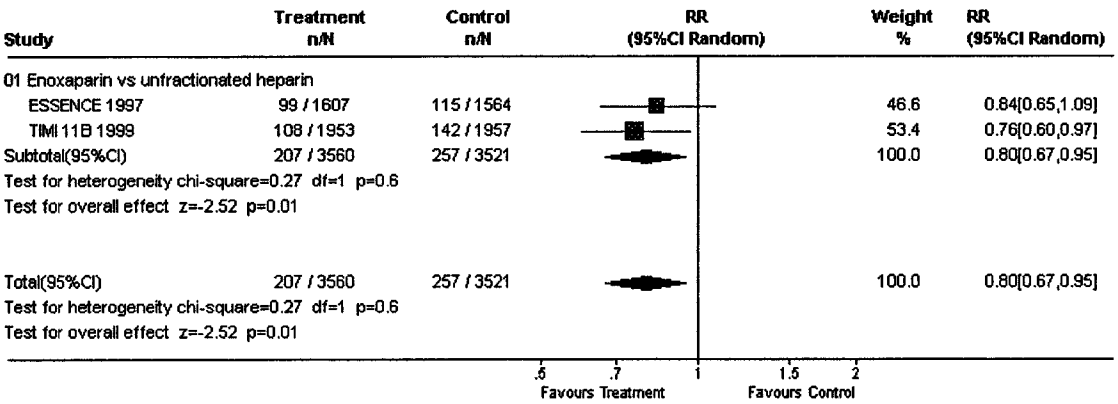


Figure 3.15: Comparison of LMWH to controls with UFH and its effect on multiple end points (3-14 days).

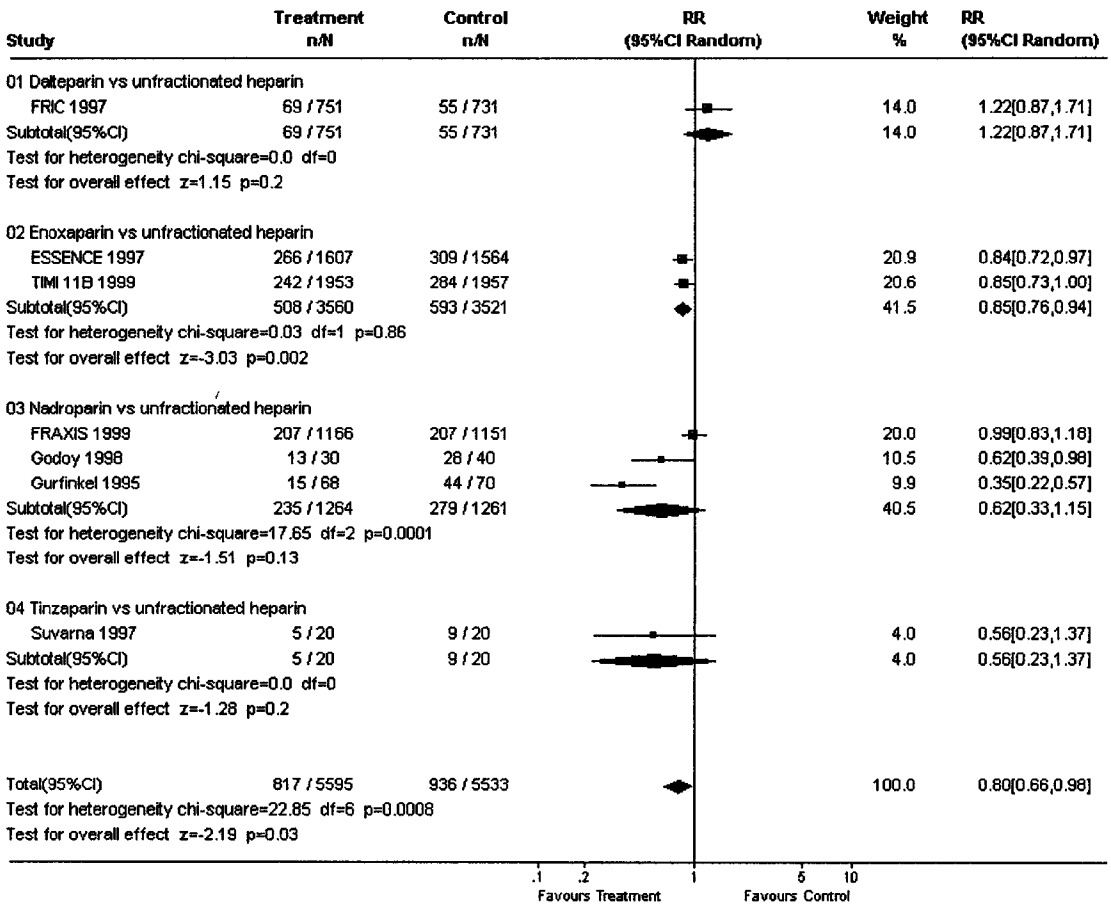


Figure 3.16: Comparison of LMWH to controls with UFH and its effect on multiple end points (> or = 30 days).

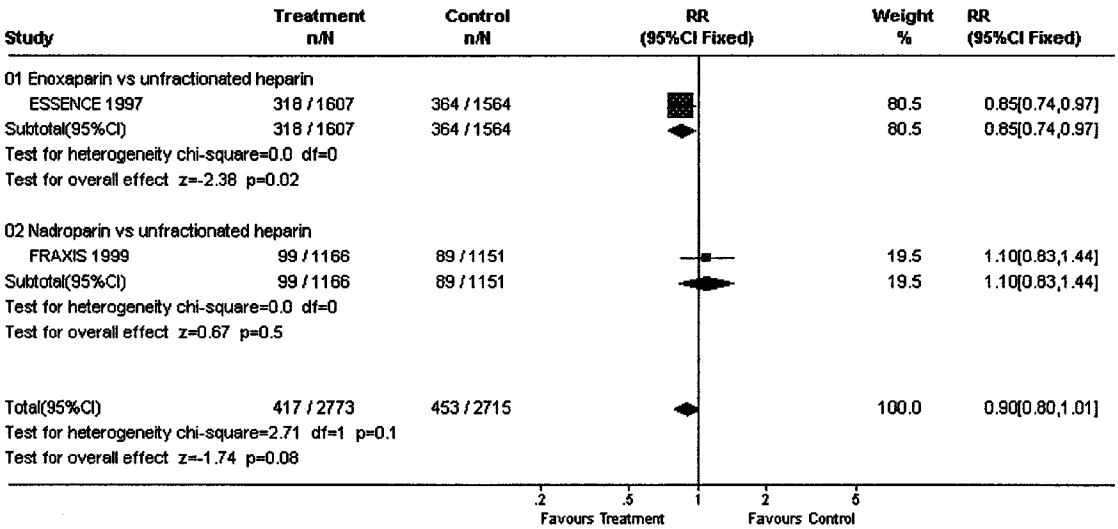


Figure 3.17: Comparison of LMWH to controls with UFH and its effect on major bleeds.

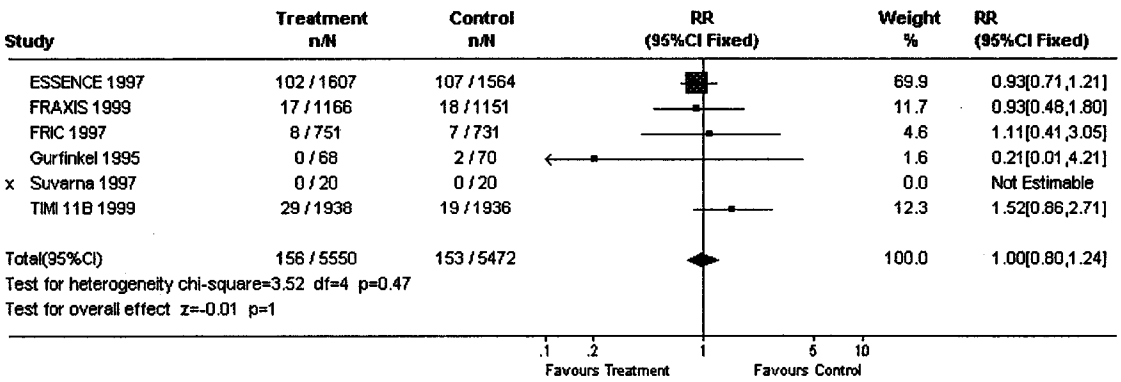


Figure 3.18: Comparison of LMWH to controls with UFH and its effect on minor bleeds.

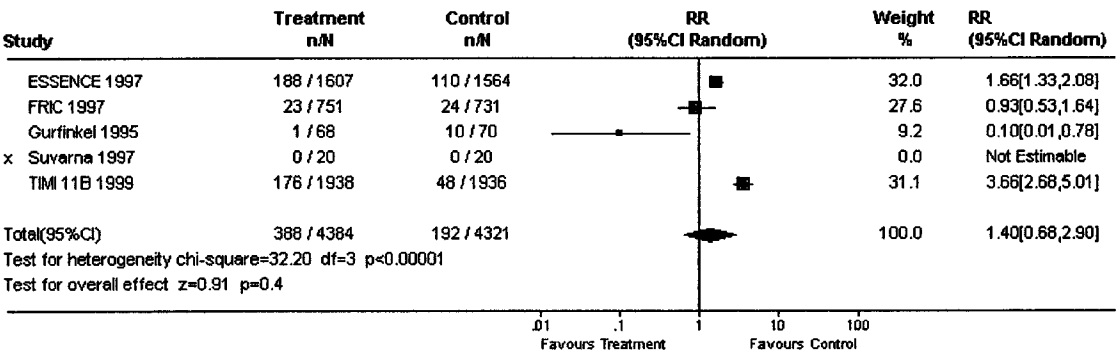
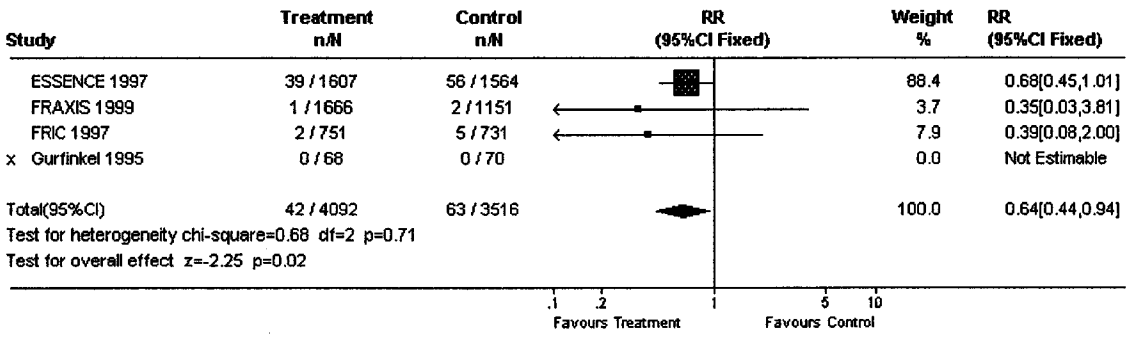


Figure 3.19: Comparison of LMWH to controls with UFH and its effect on thrombocytopenia.



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Chapter Four

Discussion

4.1 Introduction

Acute coronary syndromes (ACS) are common presentations to the ED requiring rapid diagnosis and treatment by Emergency Physicians. The literature is replete with extensive trials and numerous consensus statements on the early management of ACS. Despite this, numerous controversies regarding the best management of these patients remain. In part, this may be due to the very nature of medicine itself and the development and dissemination of evidence. "Truths", once established, are very difficult to change. The early use of anticoagulants, specifically heparin compounds (UFH and LMWH), in the treatment of unstable angina (UA) is one such example. One meta-analysis which showed a non-significant *trend* towards reduction in mortality and MI(1) became the cornerstone for national consensus guidelines.

With the advent of newer anti-thrombin therapies, clinicians and trialists re-evaluated the role of heparins in the early treatment of ACS and sought to determine whether LMWH should replace UFH in the new treatment approach. Given the equivocal outcomes of earlier studies examining UFH and the number of newer studies involving LMWH, the meta-analysis represented a valuable tool to answer these questions. Using the rigid methodology endorsed by the Cochrane Collaboration, this thesis examined the use of heparins in the early treatment of ACS in the form of two systematic reviews: the first examined all

heparins versus placebo in the early management of ACS and the second specifically addressed LMWHs versus UFH in ACS.

The two reviews established what is known about the use of heparins early in the treatment of ACS. Although they have helped to establish the best available evidence to guide clinical decision-making, several questions remain unanswered. The overall conclusions and future research implications will be discussed at the end of this chapter.

4.2 The Early Use of Heparins in ACS

This systematic review comparing *any* heparin to ASA included eight studies involving 3110 enrolled patients. Only those studies where both the control and the experimental group received standard ASA therapy were included in the meta-analysis. This represents two additional trials (2,3) with 1757 more subjects than the initial meta-analysis by Oler *et al* in 1996. The latest study included in the review involved an additional 191 patients randomized to treatment with heparin versus placebo who presented with unstable angina within 2 weeks to 6 months after coronary angioplasty. The FRISC trial published in 1996 represents the most significant contribution to this newest systematic review. FRISC enrolled 1506 patients with unstable coronary artery disease, nearly half of all subjects included in the systematic review, who were randomized in a double-blind fashion to receive the a LMWH (dalteparin) versus placebo.(2)

Nearly 75% of patients were enrolled in four trials of high methodological quality. As a group, heparins failed to show a statistically significant reduction in mortality compared to placebo. Heparins did, however, decrease the occurrence of MI such that 33 patients needed to be treated with heparin to prevent 1 additional MI. Two of the eight included studies compared LMWH to placebo. Only the LMWH subgroup showed a statistically significant benefit in any of the outcomes studied. This improvement in outcome was not accompanied by a clinically significant increase in morbidity. Although there were more minor bleeds and a trend toward more major bleeds in the heparin treated group, this did not reach the level of statistical significance.

4.3 UFH Compared to LMWH in ACS

Evidence for the use LMWH compared to UFH arises from seven studies looking at 4 different LMWH compounds. The majority of the subjects (84%) were enrolled in trials of high methodological quality. All patients received concomitant ASA and standard anti-anginal therapy. Although there were variations in the LMWH used, the timing of the intervention and the follow-up periods, little heterogeneity was identified in the summary outcomes. Because of this and the class effect observed among different preparations of LMWH in the treatment of venous thromboembolic disease, we believe it was appropriate to pool the data from the various studies.

Once again, no statistically or clinically important difference was demonstrated between the experimental and the control group with respect to

mortality. There were, however, both statistically and clinically significant improvements in other outcomes with LMWH treatment compared to UFH. LMWH reduced the occurrence of MI and the need for revascularization procedures while at the same time having fewer important side effects. While there were no differences in the rate of bleeding between the two groups, subjects who received LMWH had a lower rate of thrombocytopenia, a rare but life-threatening condition, compared to those who received UFH.

4.4 Implications for Research

4.4.1 Methodological Issues

Both systematic reviews raised several clinical and methodological issues. Outcomes in cardiovascular trials tend to be well defined and are often dichotomous, lending themselves well to the statistical pooling techniques available in a meta-analysis. However, trialists often failed to report a comprehensive range of outcomes, especially with regard to negative outcomes such as major hemorrhage and thrombocytopenia. Additionally, the follow-up was inconsistent across the various studies making it difficult to determine the absolute benefit of a particular therapy. This lack of clear safety data is a common finding in many trials and while systematic reviews of clinical trials may identify safety differences, their failure to do so should not be reassuring. Safety clarity may emerge following examination of large cohort or database projects.

Most trials reported composite end-points. Some have raised concerns that this is misleading because clinicians are lead to believe that all individual

endpoints are effected equally when in fact, often only the most frequent (i.e. which may be the softest) endpoint is reduced.(4) Composite outcomes which include mortality and important intermediate end-points allow for comparisons of new regimens using much smaller trials which can then be tested in so-called mega-trials.(5) In clinical studies of osteoarthritis, however, composite analysis of endpoints did not increase the precision to discriminate active treatment from placebo compared to individual endpoints.(6) Others have countered that with respect to coronary artery disease, intermediate outcomes, used as part of a composite outcome, which are clinically meaningful and share the same pathophysiological basis, correlate with an adverse long-term outcome.(7) Irrespective of these arguments, authors should strive to present complete data on all endpoints.

4.4.2 Clinical Issues:

Several important questions arose from the two reviews. First, what is the optimal timing for the administration of heparins? The fifteen studies examined three different time periods: within 24, 48 and 72 hours. Although it seems intuitive that earlier is better, there is no clear evidence regarding the effect of timing on outcome. This area requires further study.

While it seems clear that LMWHs are at least as effective/efficacious as UFH and likely better in the early treatment of ACS, whether or not this is a class effect is more controversial. Enoxaparin, which was received by 63% of eligible patients, was the only LMWH to show an individual benefit compared to UFH. Without head-to-head comparisons, it is difficult to determine if this secondary to

pharmacologic differences among the LMWH or heterogeneity in study design. To date, there has only been a single head-to-head comparison of LMWHs. The EVET trial(8) was an open-labelled prospective randomized control trial comparing enoxaparin to tinzaparin administered within 24 hours to patients with non-STEMI ACS. Four hundred and thirty-eight patients with were enrolled in the study. Though the authors concluded that enoxaparin was superior to tinzaparin in reducing the primary composite endpoint of death/MI/recurrent angina (12.3% versus 21.1%; p = 0.015) there are several criticisms of this study. The difference in composite end-points was mainly driven by the difference in the rate of unstable angina. This "soft" end-point is most susceptible to the bias inherent in a non-blinded trial such as this.(9) As well, tinzaparin was administered once per day, compared to twice per day with enoxaparin and at the dose commonly used in the treatment of venothrombolic disorders. Whether the tinzaparin group may have been subtherapuetic towards the end of the day, or the dose needed to treat an **arterial** thrombotic disorder is higher, remains unclear.

With the advent of glycoprotein IIb/IIIa inhibitors and the move towards early percutaneous coronary intervention in ACS(10), the role of LMWH in the anticoagulation armamentarium remains unclear. As well, what role LMWH will play in the setting of acute ST segment elevation MI in conjunction with systemic thrombolytic therapy remains to be seen. A recent review by Wong *et al*(11) represents the first attempt to systematically compile evidence to answer these questions.

4.5 Summary for Clinicians

Since the initial meta-analysis review by Oler in 1996, there have been at least four other reviews comparing LMWH to UFH(11-14) excluding the two presented here. Their conclusions, while similar, are not identical. While most would recommend LMWH over placebo, they differ in their comparison of LMWH to UFH and whether LMWH should even be considered to have a class-effect. At the very least, they judge LMWH to be no worse than UFH in the early treatment of ACS.

The reviews presented here represent the best available evidence for the use of heparins in the early management of UA and NSTEMI compiled within the rigid methodology of the Cochrane Collaboration. As a group, heparins reduce the occurrence of MI compared to placebo with no significant increase in side-effects. When LMWHs were compared directly to UFH, patients treated with LMWH had a lower rate of MI, revascularization procedures and thrombocytopenia. Given its ease of administration and the lack of need to monitor anticoagulation profiles, it seems appropriate to recommend the early use of LMWH in patients with a history of typical angina accompanied by either a past medical history of coronary artery disease or ECG/cardiac enzyme changes. The clinician should use caution, however, when the patient may require urgent surgical intervention or in situations where the optimal dose of LMWH has not been well established. These include patients at the extremes of weight, renal insufficiency and pregnant women.(11)

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Appendix A

Protocols

Heparins versus placebo for acute coronary syndromes

and

Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes

Title: Heparins versus placebo for acute coronary syndromes.

Authorship: Kirk D Magee, David Moher, Samuel Campbell, Brian H Rowe.

1.0 BACKGROUND

Unstable angina (UA) is a common problem characterized physiologically by endovascular thrombus formation. Atherosclerotic 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.(1) Until recently, a significant proportion of patients admitted with unstable angina progressed to myocardial infarction (MI) or died in hospital.(2,3)

Given the role of thrombin in the pathogenesis of acute coronary syndromes (ACS), heparin has the potential to decrease the occurrence of these undesirable outcomes. Although recent systematic reviews have showed a trend towards improved efficacy with the addition of unfractionated heparin (UFH) to aspirin (ASA) therapy,(4) these studies have failed to show a significant reduction in death and myocardial infarction. Despite this, UFH is considered the standard accepted treatment standard for non-Q wave MI and UA(5,6) and continues to be the benchmark against which low molecular weight heparin (LMWH) and other agents is 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 ACS. Although emerging evidence suggests that LMWH is more efficacious compared to UFH,(7) there is limited data to support the role of heparin as a drug class in the treatment of ACS. This systematic review of heparins (UFH and LMWH) in the acute treatment of unstable angina and non-Q-wave MI attempts to fill that void.

We propose to perform a focused, structured meta-analysis of any heparin compared to placebo, in the early treatment of ACS. We remain convinced that this study represents a comprehensive review of this subject area.

2.0 BACKGROUND

2.1 Objectives

Is heparin more effective than placebo in the treatment of patients with acute coronary syndromes?

2.2 Questions

For patients with unstable angina, what is the effect of acute treatment heparin on:

4.2.1 death, myocardial infarction, or recurrent angina?

4.2.2 on side effects/complications?
4.2.3 on cost?

2.3 Subgroups

Two specific subgroups are planned a priori:
2.3.1 comparison of results based on whether LMWH or UFH was used.
2.3.2 unstable angina compared to non-Q wave MI.

3.0 METHODS

3.1 Criteria for Considering Trials for this Review

Study Design

To be considered, clinical studies must be randomized controlled trials.

Population

Only studies which include adult patients (> 18 years of age) presenting with acute coronary syndromes requiring treatment within 24 hours of presentation. Acute coronary syndromes include unstable angina and non-Q wave MI. UA is 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-Q wave MI refers to chest pain with ST segment depression and elevation of relative cardiac enzymes (CK-MB greater than the upper normal limit or total CK greater than twice the usual upper limit). Those studies where the patients were inpatients, had stable angina, were volunteers, or presented to non-ED settings will be excluded.

Interventions

All patients must receive standard ASA therapy and be randomized to receive treatment with either intravenous heparin or placebo within 24 hours of presentation.

Outcomes

All studies must report clinically relevant outcomes. Outcomes will include:

- death
- MI
- recurrent angina (anginal chest pain that requires nitroglycerin infusion to be restarted)
- revascularization
- major hemorrhage(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 (any clinically important bleed that does not qualify as major; e.g. epistaxis, ecchymosis or hematoma, or macropscopic hematuria)
- thrombocytopenia (platelet count $<100x10^9/L$)
- allergic reactions

3.2 Search Strategies for the Identification of Trials

A comprehensive search of EMBASE, MEDLINE, CINHAL and the Cochrane Controlled Trials Registry will be completed. There will be no language or publication restrictions and no publication status restrictions. The search will consist 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 will be reviewed to identify potential relevant citations. Inquires regarding other published or unpublished studies known and/or supported by the authors of the primary studies will be made so that these results may be included in this review. Scientific advisors of the various pharmaceutical industries that manufacture LMWH will be contacted for any unpublished or interim results on the acute use of LMWH on patients with unstable angina. Finally, personal contact with colleagues, collaborators and other trialists working in the field of acute coronary syndromes will be made to identify potentially relevant studies.

3.4 Methods of Review

In Phase I, all trials which appear relevant on the basis of 'Title', 'Abstract', and 'MeSH Headings' will be selected for full review by two reviewers (BHR, KM).

In Phase II, from the potentially relevant articles in Phase I, two reviewers will independently select trials (based on the full text format) for inclusion in this review (see the appendix for inclusion criteria). Agreement will be measured using simple agreement and kappa statistics. Disagreement will be resolved by consensus or third party adjudication. Independent reviewers will document the content of each included study.

The methodological quality assessment will be performed using two methods and independently by two reviewers. The abstractors will not be blinded to the authors or the results of the study. However, we propose to perform a piloting study of the two methods of quality assessment, followed by an observer reliability study. An acceptable level of agreement must be 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,(8) all trials will be scored and entered using the following principals: Grade A: Adequate concealment; Grade B: Uncertain; Grade C: Clearly inadequate concealment. Inter-rater reliability will be measured by using kappa weighted statistics. In addition, each study will be assessed using a 0-5 scale described by Jadad.(9)

Data for the trials will be extracted independently by two reviewers (BHR, KM) and entered into the Review Manager software program. Data extraction will include the following items:

Population: age, gender, time to presentation, inclusion and exclusion criteria.
Intervention: agent, dose, duration of therapy,
Control: UFH dose, weight-based Vs fixed dosing, duration, target aPTT, time to adequate aPTT.
Outcome: timing of primary outcome, assessors, adjudication, definition of: MI, U/A, mortality. Side effect designation of minor and major bleeding.
Design: parallel group Vs cross-over, method of randomization,

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

3.4 Statistical Considerations

An intention-to-treat analysis will be completed which deals with the "missing data" issues from the individual trials. If a publication bias is present, the results will be adjusted using the Egger approach and the "trim and fill" one. In addition, quality weighting will be used to test the robustness of the results.

All trials will be combined using the Review Manager. For dichotomous variables, individual and pooled statistics will be calculated as odds ratios (OR) with 95% confidence intervals (95% CI); a random effects model will be used. For continuous outcomes individual and pooled statistics will be calculated as weighted mean differences (WMD) or standardized mean differences (SMD) and 95% CIs using a random effects model.

Subgroups: Two specific subgroups are planned a priori. One will compare unstable angina to non-Q wave MI. The second will compare results based on whether UFH or LMWH was used. Other sensitivity analyses will be conducted on mixed vs. random effects and methodological quality (high vs. low).

Sensitivity Analyses: If significant heterogeneity ($p < 0.1$) exists, the groups will 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 vs. unstable angina and non Q-wave MI;
c) Intervention: UFH vs. LMWH.

3.5 Dissemination

Upon completion, plans are being made to present the results at the 2001 CAEP Annual Scientific Meeting and to submit the results for publication.

4.0 TIME FRAME

The overview will take approximately 6 months to complete given the time allocated to the research assistant. The first three months will be used to complete the search strategy and obtain manuscripts. The next month will be used to coordinate the selection of included studies and to code the papers for validity. The final two month will be spent entering all information into the Reference Manager, conducting statistical analysis and generating a draft of the report.

5.0 FUTURE PLANS

The data may be used to develop a survey for the CAEP Research Consortium on the treatment of acute coronary syndromes in the ED.

6.0 GLOSSARY

ACS – Acute Coronary Syndromes

ASA – Acetylsalicylic Acid
HIT – Heparin Induced Thrombocytopenia
MI – Myocardial Infarction
LMWH – Low Molecular Weight Heparin
UA – Unstable Angina
UH – Unfractionated Heparin
VTE – Venous Thromboembolism

7.0 REFERENCES

1. Fuster V. Elucidation of the role of plaque instability and rupture in acute coronary events. Am J Cardiol 1995;76:24C-33C.
2. Cairns JA, Singer J, Gent M, et al. One year mortality outcomes of all coronary and intensive care unit patients with acute myocardial infarction, unstable angina or other chest pain in Hamiliton, Ontario, a city of 375,000 people. Can J Cardio 1989;319:239-46.
3. Cohen M. Approaches to the treatment of unstable angina and non-Q wave myocardial infarction. Can J Cardio 1998;14(Suppl E):11E-14E.
4. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the Incidence of myocardial infarction and death in patients with unstable angina: a meta-analysis. Lancet 1996;276:811
5. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med 1988;319:1105-11.
6. The RISC Group. Risk of myocardial infarction and death during treatment with low-dose aspirin and intravenous heparin in men with unstable coronary artery disease. Lancet 1990;336:837-30.
7. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. Lancet 2000;355:1936-42.
8. Section VI: Preparing and maintaining systematic reviews. Cochrane Collaboration Handbook, Oxford University Press, Oxford. 1994.
9. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996;17:1-12.

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

Authorship: Kirk D Magee, William Sevcik, David Moher Brian H Rowe.

1.0 BACKGROUND

Unstable angina (UA) is characterized by endovascular thrombus formation. It is thought that atherosclerotic plaque disrupts resulting in the activation of the coagulation and platelet system with subsequent formation of a labile thrombus causing a temporary occlusion of the coronary arteries lasting from 10 to 20 minutes.(1) Until recently, a significant proportion of patients admitted with unstable angina progressed to myocardial infarction (MI) or died in hospital.(2)

Despite the weak evidence for the use of unfractionated heparin (UFH) in acute coronary syndromes, it is now considered the accepted treatment standard for non-Q wave MI and unstable angina.(3,4) Unfortunately, there are many problems with its use. Even with ASA and UFH combination therapy, there is still a 20% failure rate (death, MI or recurrent angina) at three months.(5) As well, agreement on the diagnosis of UA is not perfect. Many patients, therefore, receive unnecessary and potentially harmful treatment while those who need it may go without. Another problem is that UFH has a variable dose response requiring repeated monitoring of patients' coagulation profiles. It is not uncommon for patients to be sub-therapeutic many hours after the initiation of treatment.(6) Furthermore, with UFH there is the significant risk of hemorrhagic complications and immune-mediated heparin-induced thrombocytopenia (HIT).

Low molecular weight heparins (LMWHs) are produced by the depolymerization of standard UFH into smaller fragments.(7) LMWHs 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.(8) Traditionally, LMWHs have been considered to be equivalent to UFH in ACS and venous thromboembolism (VTE) and cost has been cited as a reason for the continued use of UFH. However, recent systematic review have demonstrated that LMWHS are safer and more efficacious in the treatment of VTE.(9-11)

Currently, there is a great deal of interest in the use of LMWH in the treatment of ACS given its more favourable therapeutic profile as compared to UFH. Indeed, enoxaparin has already been approved in the United States for use with unstable angina and non-Q wave MI. Despite numerous studies comparing LMWH versus UH, the various trials have used different doses and regimes for both LMWH and UH which makes comparisons difficult without a formal meta-analysis. Although there have been numerous reviews regarding the use of LMWH in ACS, they have, through their methodological limitations,

lacked the power of a formal meta-analysis. This systematic review of LMWH in the acute treatment of unstable angina aims to fill that void.

In view of the numerous clinical trials examining the role of LMWHs in the treatment of acute coronary syndromes, we propose to perform a focused, structured meta-analysis of LMWH versus UFH, in the early treatment of unstable angina. We remain convinced that this study represents a comprehensive review of this subject area.

2.0 RESEARCH QUESTION

2.1 Objectives

Is LMWH more effective than UH in patients with acute coronary syndromes?

2.2 Qustions

For patients with unstable angina, what is the effect of acute treatment with low molecular weight heparin on:

4.2.1 death, myocardial infarction, or recurrent angina?
4.2.2 on side effects/complications?
4.2.3 on cost?

2.3 Subgroups

Two specific subgroups are planned a priori:

2.3.1 unstable angina compared to non-Q wave MI.
2.3.2 comparison of results based on the specific LMWH used.

3.0 METHODS

3.1 Criteria for Considering Trials for this Review

Study Design

To be considered, clinical studies must be randomized controlled trials.

Population

Only studies which include adult patients (> 18 years of age) presenting with acute coronary syndromes requiring treatment within 24 hours of presentation. Acute coronary syndromes include unstable angina and non-Q wave MI. UA is 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-Q wave MI refers to chest pain with ST segment depression and elevation of relative cardiac enzymes (CK-MB greater than the upper normal limit or total CK greater than twice the usual upper limit). Those studies where the patients were inpatients, had stable angina, were volunteers, or presented to non-ED settings will be excluded.

Interventions

All patients must be randomized to receive treatment with either parentral LMWH or intravenous UFH within 24 hours of presentation.

Outcomes

All studies must report clinically relevant outcomes. Outcomes will include:

- death
- MI
- recurrent angina (anginal chest pain that requires nitroglycerin infusion to be restarted)
- revascularization
- major hemorrhage(fall in hemoglobin level of >20 g/L, requires transfusion, is intracranial, retroperitoneal, or intraocular, or causes death or ceasation of the study treatment)
- minor hemorrhage (any clinically important bleed that does not qualify as major; e.g. epistaxis, ecchymosis or hematoma, or macroscopic hematuria)
- thrombocytopenia (platelet count $<100x10^9/L$)
- allergic reactions

3.2 Search Strategies for the Identification of Trials

A comprehensive search of EMBASE, MEDLINE, CINHAL and the Cochrane Controlled Trials Registry will be completed. There will be no language or publication restrictions and no publication status restrictions. The search will consist 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 tinzapain 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 will be reviewed to identify potential relevant citations. Inquires regarding other published or unpublished studies known and/or supported by the authors of the primary studies will be made so that these results may be included in this review. Scientific advisors of the various pharmaceutical industries that manufacture LMWH will be contacted for any unpublished or interim results on the acute use of LMWH on patients with unstable angina. Finally, personal contact with colleagues, collaborators and other trialists working in the field of acute coronary syndromes will be made to identify potentially relevant studies.

3.3 Methods of Review

In Phase I, all trials which appear relevant on the basis of 'Title', 'Abstract', and 'Mesh Headings' will be selected for full review by two reviewers (BHR, KM).

In Phase II, from the potentially relevant articles in Phase I, two reviewers will independently select trials (based on the full text format) for inclusion in this review (see the appendix for inclusion criteria). Agreement will be measured using simple agreement and kappa statistics. Disagreement will be resolved by

consensus or third party adjudication. Independent reviewers will document the content of each included study.

The methodological quality assessment will be performed using two methods and independently by two reviewers. The abstractors will not be blinded to the authors or the results of the study. However, we propose to perform a piloting study of the two methods of quality assessment, followed by an observer reliability study. An acceptable level of agreement must be 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,(12) all trials will be scored and entered using the following principals: Grade A: Adequate concealment; Grade B: Uncertain; Grade C: Clearly inadequate concealment. Inter-rater reliability will be measured by using kappa weighted statistics. In addition, each study will be assessed using a 0-5 scale described by Jadad.(13)

Data for the trials will be extracted independently by two reviewers (BHR, KM) and entered into the Review Manager software program. Data extraction will include the following items:

Population: age, gender, time to presentation, inclusion and exclusion criteria.
Intervention: agent, dose, duration of therapy,
Control: UFH dose, weight-based Vs fixed dosing, duration, target aPTT, time to adequate aPTT.
Outcome: timing of primary outcome, assessors, adjudication, definition of: MI, U/A, mortality. Side effect designation of minor and major bleeding.
Design: parallel group Vs cross-over, method of randomization,

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

3.4 Statistical Considerations

An intention-to-treat analysis will be completed which deals with the "missing data" issues from the individual trials. If a publication bias is present, the results will be adjusted using the Egger approach and the "trim and fill" one. In addition, quality weighting will be used to test the robustness of the results.

All trials will be combined using the Review Manager. For dichotomous variables, individual and pooled statistics will be calculated as odds ratios (OR) with 95% confidence intervals (95% CI); a random effects model will be used. For continuous outcomes individual and pooled statistics will be calculated as weighted mean differences (WMD) or standardized mean differences (SMD) and 95% CIs using a random effects model.

Subgroups: Two specific subgroups are planned a priori. One will compare unstable angina to non-Q wave MI. The second will compare results

based on the specific LMWH used. Other sensitivity analyses will be conducted on mixed vs. random effects and methodological quality (high vs. low).

Sensitivity Analyses: If significant heterogeneity ($p < 0.1$) exists, the groups will 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 vs. unstable angina and non Q-wave MI;

c) Intervention: different types of LMWH.

3.5 Dissemination

Upon completion, plans are being made to present the results at the 1999 CAEP Annual Scientific Meeting and to submit the results for publication.

4.0 TIME FRAME

The overview will take approximately 6 months to complete given the time allocated to the research assistant. The first three months will be used to complete the search strategy and obtain manuscripts. The next month will be used to coordinate the selection of included studies and to code the papers for validity. The final two month will be spent entering all information into the Reference Manager, conducting statistical analysis and generating a draft of the report.

5.0 FUTURE PLANS

Future plans include doing a formal cost-analysis of the use of LMWH for the emergency department treatment of unstable angina at the University of Alberta. In addition, data may be used to develop a survey for the CAEP Research Consortium on the treatment of acute coronary syndromes in the ED.

6.0 GLOSSARY

ACS – Acute Coronary Syndromes

ASA – Acetylsalicylic Acid
HIT – Heparin Induced Thrombocytopenia
MI – Myocardial Infarction
LMWH – Low Molecular Weight Heparin
UA – Unstable Angina
UH – Unfractionated Heparin
VTE – Venous Thromboembolism

7.0 REFRENCES

1. Fuster V. Elucidation of the role of plaque instability and rupture in acute coronary events. Am J Cardiol 1995;76:24C-33C.
2. Cairns JA, Singer J, Gent M, et al. One year mortality outcomes of all coronary and intensive care unit patients with acute myocardial infarction, unstable angina or other chest pain in Hamiliton, Ontario, a city of 375,000 people. Can J Cardio 1989;319:239-46
3. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med 1988;319:1105-11.
4. The RISC Group. Risk of myocardial infarction and death during treatment with low-dose aspirin and intravenous heparin in men with unstable coronary artery disease. Lance 1990;336:837-30.
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6. Antman EM. Hirudin in acute myocardial infarction. Thrombolysis and thrombin inhibition in myocardial infarction (TIMI) 9B trial. Circulation 1996;94:911-21.
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11. The Columbus Investigators. Low molecular weight heparin is an effective and safe treatment for deep-vein thrombosis and pulmonary embolism. New Engl J Med 1997;337:657-662.
12. Section VI: Preparing and maintaining systematic reviews. Cochrane Collaboration Handbook, Oxford University Press, Oxford. 1994.
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Appendix B

Data Extraction forms

ALL HEPARINS VERSUS PLACEBO FOR THE ED TREATMENT OF UNSTABLE ANGINA, NON-ST SEGMENT MI

CRITERIA FOR INCLUSION

Citation # _____

Reviewer: BR KM

Please assess the following questions for each paper. **WHEN YOU OBTAIN ONE X (NOT INCLUDED) STOP.** The inclusion criteria are:

[1] DESIGN

[ ] Randomized controlled clinical trial on adults (>18 years of age).

[ ] **Exclude** all studies which are non-experimental (cohort study, case-control study, before-after studies, case series, letters, reviews, etc.).

[2] POPULATIONS

[ ] Include if patients were selected due to unstable angina and/or non-ST segment MI requiring treatment within 72 hours of symptom onset or of presentation.

[ ] **Exclude** papers where the patients were inpatients, had stable angina, were volunteers, or presented to non-ED settings.

[3] INTERVENTIONS

[ ] Include all primary research in which patients were treated with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) versus placebo within 72 hours of presentation.

[ ] **Exclude** if LMWH or UFH was not the primary research question or if LMWH or UFH was started after admission.

[4] OUTCOMES

[ ] Must have clinically relevant outcomes (i.e. death, MI, recurrent angina, hemorrhage) or economic outcomes.

[ ] **Exclude** all studies that do not report clinically relevant or economic outcomes.

[5] FINAL DECISION

[ ] INCLUDED (meets inclusion criteria above)
[ ] NOT INCLUDED
[ ] CAN'T TELL (need more information from authors to make decision)

LOW MOLECULAR WEIGHT HEPARIN VERSUS UNFRACTIONATED HEPARIN FOR THE ED TREATMENT OF UNSTABLE ANGINA

METHODOLOGICAL QUALITY ASSESSMENT

Citation # _____

Reviewer: BR KM

Jadad Criteria:

1) Was the study described as randomized?
[ ]Yes [ ]No
2) Was the study described as double-blind?
[ ]Yes [ ]No
3) Was there a description of withdrawals and dropouts?
[ ]Yes [ ]No
4) Was the method of randomization well described and appropriate?
[ ]Yes [ ]No
5) Was the method of double blinding well described and appropriate?
[ ]Yes [ ]No
6) Deduct 1 point if methods for randomization or blinding were inappropriate.

Total Score (out of 5): _____ (Yes=1, No=0)

Cochrane Criteria

[ ]Grade A: Adequate concealment
[ ]Grade B: Uncertain
[ ]Grade C: Clearly inadequate concealment

Appendix C

Letter to Authors

June 25th, 1999

Dear Dr.

RE: Low molecular weight heparin use in acute coronary syndromes: A systematic review of the literature.

The Cochrane Collaboration of Systematic Reviews is a multi-disciplinary, collaborative volunteer organization whose mandate is to produce and disseminate overviews on a variety of medical topics. One of the large interest areas of the Cochrane Collaboration is cardiovascular diseases, and recently the Cochrane HEART Group was registered. We are members of the group and we are particularly interested in conducting systematic reviews involving acute cardiovascular diseases such as myocardial infarction, atrial fibrillation, angina, etc.

We are in the process of completing a meta-analysis on the effect of low molecular weight heparin (LMWH) in the treatment of patients with acute coronary syndromes. This review has been accepted for protocol development and will eventually be published on the Cochrane Collaboration's main resource, the *Cochrane Library*. We are specifically interested in randomized controlled trials where LMWH is used early in the treatment of unstable angina and non-Q-wave myocardial infarction, and compared to unfractionated heparin.

Your work, entitled:

has been selected for inclusion in our meta-analysis. The research collaborators have also independently selected the articles shown on the accompanying sheet for inclusion. We are writing to you for several reasons. First, we wonder if you could provide additional references for published or unpublished research which might deserve inclusion in this overview. Secondly, as part of the Cochrane Collaboration methodology, we are interested in having the authors of included studies provide us with feedback on the data extracted from their article. As you can imagine, valid and reliable data extraction is necessary for the final version of the overview, which will be available on the Cochrane Library CD-ROM and disks. The responses we receive from authors will be acknowledged in the final "comments" section for every included study.

We look forward to hearing from you. Would you be so kind as to complete the following form and FAX it back to us as soon as it is convenient with you? The FAX

number is (780) 407-3314. Thank you in advance for your attention to these matters.

Yours sincerely,

Kirk Magee, MD, FRCPC PGY-5 Resident
Division of Emergency Medicine, University of Alberta
MSc Candidate
kmagee@ualberta.ca

Brian H. Rowe, MD, MSc, CCFP(EM)
Research Director, Division of Emergency Medicine
Associate Professor, University of Alberta
Brian.Rowe@ualberta.ca

Low molecular weight heparin in acute coronary syndromes—Meta-analysis

Name:

Title:

Are you aware of any additional studies that relate to the above mentioned papers?

☐ Yes ☐ No

If yes, please list:
1._____
2._____
3._____
4._____

Would you be able to provide feedback with respect to data extracted from your article?

☐ Yes, please contact me at this fax number/email _____.

☐ No, however, _____ would be able to provide this service to your research team. He/she can be contacted at the following address, email and/or fax number:

_____
_____
_____

☐ No, I would not be able to provide feedback to you.

The following articles have been included in the meta-analysis:

Antman EM. TIMI 11B. Enoxaparin versus unfractionated heparin for unstable angina or non-Q-wave myocardial infarction: a double-blind, placebo-controlled, parallel-group, multicenter trial. Rationale, Study design, and methods. Thrombolysis in Myocardial Infarction (TIMI) 11B Trial Investigators. Am Heart J. 1998;135:S353-S360.

Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S et al. A comparison of low molecular weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaprin in Non-Q-Wave Events Study Group. N Engl J Med. 1997;337:447-52.

Gurfinkel EP, Manos EJ, Mejail RI, Cerda MA, Duronto EA, Garcia CN et al. Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. J Am Coll Cardiol. 1995;26:313-18.

Klein W, Buchwald A, Hillis WS, Monarad S, Sanz G, Turpie AG et al. Comparison of low molecular weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). Circulation. 1997;96:61-68.

Suvarna TT, Parikh JA, Keshav R, Pillai MG, Gandhi MJ. Comparison of clinical outcome fixed-dose subcutaneous low molecular weight heparin (tinzaparin) with conventional heaprin in unstable angina: a pilot study. Indian Heart J. 1997;49:159-62.

The following articles are being considered for inclusion in the meta-analysis:

Bednarkiewicz, Z., Krzeminska-Pakula, M., Kurpesa, M., Trzos, E., Peruga, J., and Religa, W. Low molecular weight heparin vs regular heparin in the treatment of patients with unstable angina. Journal of the American College of Cardiology (Suppl), 409A. 1997.

Claudio Correia LC, Neubauer C, Azevedo A, Jr., Ribeiro F, Braga J, Carlos Passos L et al. The role of low molecular weight heparin in unstable angina, acute myocardial infarction and post-elective percutaneous transluminal coronary angioplasty. Arq Bras Cardiol. 1995;65:475-78.

Correia, L., Esteves, F., Rocha, M., and Esteves, J. P. Comparison between low molecular weight heparin and standard heparin in unstable angina. Journal of the American College of Cardiology (Suppl), 326A. 1996.

Godoy I, Herrera C, Zapata C, Kunstmann S, Abufhele A, Corbalan R. Comparison of low molecular weight heparin and unfractionated heparin in the treatment of unstable angina. Rev Med Chil. 1998;126:259-64

The following articles have been excluded from the meta-analysis:

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