ARTICLE

The Use of Low-Molecular-Weight Heparins in Acute Coronary Syndromes

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ABSTRACT

Low-molecular-weight heparins are an attractive alternative to unfractionated heparin in many areas of anticoagulation therapy. Recently, their use in acute coronary syndromes has been studied. Low-molecular-weight heparins are fragments of unfractionated heparin with a mean molecular weight of 5000 daltons. Their advantages include minimal binding to plasma proteins, lower frequency of thrombocytopenia, longer half-life, and minimal requirement for laboratory monitoring. At present, 2 low-molecular-weight heparins, dalteparin and enoxaparin, are approved in Canada for use in unstable angina.

This paper reviews the main trials conducted in acute coronary syndromes. The recently published results of the TIMI (Thrombolysis in Myocardial Infarction) 11B trial have confirmed the earlier findings of the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events) trial, which demonstrated that enoxaparin was more effective than unfractionated heparin in preventing a composite endpoint of death, myocardial infarction and recurrent angina. The FRAX.I.S. (Fraxiparine in Ischaemic Syndrome) trial and the FRISC (Fragmin during Instability in Coronary Artery Disease) II trial demonstrated that nadroparin and dalteparin are equivalent in efficacy to unfractionated heparin for the treatment of acute coronary syndromes.

Given that only enoxaparin has efficacy superior to that of unfractionated heparin, it would be the low-molecular-weight heparin of choice when considering additions to the hospital formulary. Restrictions should be implemented, including limitation of use in morbidly obese patients, those in whom reversibility of the anticoagulant effect is necessary, and those with renal impairment.

In summary, enoxaparin is associated with a significant reduction in cardiac events relative to unfractionated heparin and has the advantages of less need for laboratory monitoring, lower frequency of thrombocytopenia, and similar overall cost.

Key words: low-molecular-weight heparins, acute coronary syndromes, unstable angina, dalteparin, enoxaparin, nadroparin

RÉSUMÉ

Les héparines de faible poids moléculaire (HFPM) constituent une solution de rechange alléchante à l'héparine non fractionnée pour de nombreuses applications de l'anticoagulothérapie. Dernièrement, leur usage dans les syndromes coronariens aigus a été étudié. Les HFPM sont des fragments d'héparine non fractionnée ayant une masse atomique moyenne de 5000 daltons. Une faible fixation aux protéines plasmatiques, une fréquence moindre de thrombocytopénie, une demi-vie supérieure et un minimum d'épreuves de laboratoires sont parmi leurs avantages. Actuellement, deux HFPM, la daltéparine et l'énoxaparine, sont approuvées pour usage au Canada dans l'angor instable.

Cet article examine les principales études qui ont été menées chez des patients souffrant de syndromes coronariens aigus. Les résultats de l'étude TIMI (Thrombolysis in Myocardial Infarction) 11B publiés dernièrement ont corroboré les observations issues de l'essai ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events). En effet, ils ont montré que l'énoxaparine était plus efficace que l'héparine non fractionnée dans la prévention de la morbi-mortalité globale — décès, infarctus du myocarde et angor récidivant. L'étude FRAX.I.S (Fraxiparine in Ischemic Syndrome) et l'étude FRISC (Fragmin in Unstable Coronary Artery Disease) II ont montré que la nadroparine et la daltéparine sont aussi efficaces que l'héparine non fractionnée pour le traitement des syndromes coronariens aigus.

Étant donné que seule l'énoxaparine présente une efficacité supérieure à celle de l'héparine non fractionnée, l'énoxaparine constitue donc une solution de choix si on envisage des ajouts au formulaire. Des restrictions cependant s'imposent, y compris un recours limité dans les cas d'obésité morbide, chez les patients dont une inversion rapide de l'effet anticoagulant est nécessaire, et chez les insuffisants rénaux.

En résumé, l'énoxaparine est associée à une réduction notable des événements cardiaques comparativement à l'héparine non fractionnée, et elle a l'avantage d'exiger moins d'épreuves de laboratoire, de causer moins de thrombocytopénie et d'engendrer des coûts globaux semblables.

Mots clés : héparines de faible poids moléculaire, syndromes coronariens aigus, angor instable, daltéparine, énoxaparine, nadroparine

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INTRODUCTION

Unstable angina is one of the most frequent causes of cardiovascular-related admissions to hospitals.[1] Within 1 year, approximately 10% of patients with unstable angina will experience acute myocardial infarction or will die.[2] Unfractionated heparin and acetylsalicylic acid (ASA) are generally considered the gold standard treatments for acute unstable angina. The role of low-molecular-weight heparins instead of unfractionated heparin in the treatment of unstable angina has recently been explored.

PATHOPHYSIOLOGY AND DIAGNOSIS

Unstable angina results from decreased perfusion to the myocardium at rest. It typically occurs as the result of disruption of an atherosclerotic plaque. This disruption leads to the release of tissue factor, which activates the coagulation cascade. In addition, the newly exposed collagen of the subintima allows for the adhesion and aggregation of platelets, which then activate thrombin and fibrin formation. The end result is clot formation due to the initiation of both the coagulation cascade and platelet aggregation.[3] This clot causes temporary occlusion of a coronary vessel. In unstable angina, the occlusion usually only lasts 10 to 20 min. Typically, there is little or no myocardial necrosis. In non-Q wave myocardial infarction, there is more severe plaque formation, and the occlusion lasts up to 1 h.[4]

Unstable angina is diagnosed if the patient exhibits one or more of the following criteria: angina occurring at rest and lasting more than 15 to 20 min; new onset (within the past 4 to 8 weeks) of exertion-induced class III or IV angina; previously stable angina that has increased in severity, frequency, or duration or is less responsive to nitroglycerin; and finally, angina that occurs within 1 month of myocardial infarction.[2,5] The only way to distinguish unstable angina from non-Q wave myocardial infarction is the presence of creatinine kinase-MB and troponins I and T in the serum.[6] Such laboratory results are not available when a patient is first admitted and treated in the emergency department. For this reason, in many cases unstable angina and non-Q wave myocardial infarction are initially treated in the same way. As such, both are found in the trials mentioned below under the umbrella diagnosis of unstable coronary artery disease or acute coronary syndromes.[1]

MANAGEMENT

Several different agents are used to treat unstable angina, including antiplatelet agents (such as ASA and ticlopidine), anticoagulants (such as unfractionated and low-molecular-weight heparins), and anti-ischemic therapy (such as intravenous or sublingual nitrates, ß-blockers, and calcium-channel blockers).[1,7] Non-pharmacological treatment is another option and can include percutaneous transluminal angioplasty and coronary artery bypass graft.[1] This review focusses on the use of low-molecular weight heparin in place of unfractionated heparin in the treatment of unstable angina.

Heparin and ASA

Initial treatment of unstable coronary artery disease consists of the concurrent use of heparin and ASA. The American College of Chest Physicians recommends that patients with unstable angina be given 75 U/kg unfractionated heparin IV bolus, with an initial maintenance dose of 1250 U/h, adjusted to maintain an activated partial thromboplastin time of 1.5 to 2 times the control value. The infusion should be continued for at least 48 h or until the unstable pain resolves.[7] Several studies were involved in developing this regimen. In a trial conducted by Théroux and colleagues,[8] the prevalence of myocardial infarction was lower among patients treated with only heparin for 6 days than among those treated with ASA (0.8% and 2.9%, respectively, $p = 0.035$). A meta-analysis of several studies has shown that for patients receiving both heparin and ASA, there was a 33% risk reduction in fatal and nonfatal myocardial infarction relative to those who recieved only ASA.[7] If we recall that the pathophysiology of unstable coronary artery disease involves both the activation of the coagulation cascade and platelet aggregation, it is logical that an anticoagulant and an antiplatelet agent would be needed. Théroux and colleagues also found that when heparin was used alone and then discontinued, "reactivation" of unstable angina and myocardial infarction often ensued. This "reactivation" has been attributed to a hypercoagulable state, which can persist for several months after an acute attack.[9] The combination of heparin and ASA, with continued use of ASA after the initial heparin treatment, prevented this rebound "reactivation".[9]

Low-Molecular-Weight Heparins

Unfractionated heparin is a heterogenous mixture of polysaccharide chains ranging in molecular-weight from 5000 to 30 000 daltons, whereas low-molecular-weight heparins consist of fragments of unfractionated heparin with a mean molecular weight of about 5000 daltons.[10]

Table 1. Characteristics of Various Low-Molecular-Weight Heparins*

Low-Molecular-Weight Heparin	Mean Molecular Weight (daltons)	Anti-Xa: Anti-IIa (Ratio)
Dalteparin (Fragmin)	6000	2.7:1
Enoxaparin (Lovenox)	4200	3.8:1
Nadroparin (Fraxiparine)	4500	3.6:1
Tinzaparin (Innohep)	4500	1.9:1

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Both forms bind to antithrombin III, causing a conformational change that accelerates the ability of antithrombin III to inactivate thrombin (factor IIa), factor Xa and factor IXa.[11] Because low-molecular-weight heparins are shorter in length, they are significantly less capable of simultaneously binding antithrombin III and thrombin. As such, they do not affect activated partial thromboplastin time, and monitoring of this parameter is not required. In addition, low-molecular-weight heparins preferentially bind factor Xa. Unfractionated heparin has a ratio of anti-Xa:anti-IIa activity of 1:1, whereas low-molecular-weight heparins bind preferentially to factor Xa and have anti-Xa:anti-IIa ratios of 1.5:1 to 3.9:1 (Table 1).[11,12]

One concern with these low-molecular-weight heparins is that their anticoagulant effect is not reversible, whereas the effect of unfractionated heparin can be reversed by protamine.

The main advantages of low-molecular-weight heparins over the unfractionated form include lower frequency of thrombocytopenia; minimal binding to plasma, platelet, and vessel wall proteins, which results in a more predictable and durable anticoagulant response; once-daily or twice-daily subcutaneous injections; and minimal requirement for laboratory monitoring[2,4,11-15] (Table 2). A more predictable anticoagulation response is expected with low-molecular-weight heparins because they are smaller fragments of unfractionated heparin, which are less likely to bind to other plasma proteins. Some "resistance" to unfractionated heparin has been attributed to the fact that the unfractionated form binds to the many acute-phase proteins that are released, which results in higher dosing requirements.[16] Because low-molecular-weight heparins differ in their mean molecular weight and specificity (anti-Xa to anti-IIa), they are not considered interchangeable.[17]

Currently, dalteparin, enoxaparin, nadroparin, and tinzaparin are available in Canada. Of these 4 low-molecular-weight heparins, only dalteparin and enoxaparin are officially indicated in the treatment of unstable angina.

Clinical Trials Using Low-Molecular-Weight Heparins in Unstable Angina

The trials of low-molecular-weight heparins are summarized in Table 3.

Gurfinkel and colleagues[18] evaluated the use of low-molecular-weight heparins in unstable angina to determine whether they lessen the severity of ischemic events. In this prospective, randomized, single-blind trial, 73 patients were randomly assigned to group A (ASA 200 mg daily), 70 patients to group B (ASA 200 mg daily and an IV bolus of 5000 U unfractionated heparin followed by a continuous infusion of 400 U/kg daily to achieve an activated partial thromboplastin time of 2 times control), and 68 patients to group C (ASA 200 mg daily and nadroparin 214 anti-Xa units Institute Choay (UIC)/kg SC bid). All other previous antianginal medications were continued. Patients were followed for 5 to 7 days.

The primary endpoints of the study were recurrent angina, acute myocardial infarction, urgent intervention (coronary angioplasty or bypass surgery), major bleed-

Table 2. Pharmacokinetic and Monitoring Characteristics for Unfractionated and Low-Molecular-Weight Heparins[2,4,11–15]

Characteristic	Unfractionated Heparin	Low-Molecular-Weight Heparin
Mean molecular weight (daltons)	5000 to 30 000	4000 to 5000
Plasma half-life (h)	0.5 to 4	2 to 4
Monitoring	aPTT: 1.5 to 2 times control	Anti-Xa: 0.6 to 1.0 U/mL[15]
Prevalence of heparin-induced thrombocytopenia* (% of patients)	5.7	0.9
Prevalence of bleeding (% of patients)		
In treatment of venous thromboembolism, major bleeding	0 to 7	0 to 3
In treatment of venous thromboembolism, fatal bleeding	0 to 2	0 to 0.8
In treatment of unstable angina	0.5 to 6.5	0.8 to 7.0
Agent to reverse bleeding	Protamine	None

aPTT = activated partial thromboplastin time.
* Defined as a fall in platelet count of more than 50% beginning 5 or more days after initiation of heparin therapy.

Table 3. Trials Comparing the Efficacy of Low-Molecular-Weight Heparins in Unstable Angina with Unfractionated Heparin and Acetylsalicylic Acid or Placebo

Trial	Treatment Groups and No. of Patients	Duration of Treatment	Other Concurrent Medications	Primary Endpoints	Secondary Endpoints
Gurfinkel et al (1995)[18]	*Group A (73 patients):* ASA 200 mg daily *Group B (70 patients):* ASA 200 mg daily + unfractionated heparin targeted for aPPT of 2 times control *Group C (68 patients):* ASA 200 mg daily + anti-Xa nadroparin 214 IUC/kg SC bid	5 to 7 days	Continuation of preadmission medications with drug additions or dosing adjustments prn	Major events (death, recurrent angina, AMI, major bleeding, revascularization) Group A: 59% Group B: 63% Group C: 22% (A v. C and B v. C, $p = 0.00001$)	Silent ischemia, minor bleeding Group A: 38% Group B: 56% Group C: 26.5% (A v. C, NS: B v. C, $p = 0.004$)
FRISC trial (1996)[19]	*Group A (746 patients):* dalteparin 120 U/kg SC bid *Group B (760 patients):* placebo injections	6 days, then dalteparin 7500 U SC daily (group A) or placebo injections (group B) for next 35 to 45 days	Both groups: ASA 75 mg daily + ß-blocker (CCB + organic nitrates added prn)	*At day 6* Composite outcome of death and MI Group A: 1.8% Group B: 4.8% (RR 0.37, $p = 0.001$)	*At day 40* Composite endpoint of death, new MI, need for heparin and revascularization Group A: 8.0% Group B: 10.7% (RR 0.75, $p < 0.07$)
FRIC trial (1997)[20]	*Group A (751 patients):* dalteparin 120 U/kg SC bid *Group B (731 patients):* dose-adjusted IV unfractionated heparin for 48 h or more, followed by 12 500 U SC bid	6 days, then dalteparin 7500 U SC daily (group A) or placebo injections (group B) for next 39 days	ASA 75 to 165 mg daily + other anti-anginal medications prn	*At day 45* Composite endpoint of death, MI, and recurrent angina Group A: 12.3% Group B: 12.3% (RR = 1.01)	*At day 6* Composite endpoint of death, MI, and recurrent angina: Group A: 9.3% Group B: 7.6% (RR = 1.18)
ESSENCE trial (1997)[21]	*Group A (1067 patients):* enoxaparin 1 mg/kg SC bid *Group B (1564 patients):* continuous heparin infusion targeted for aPTT of 55 to 85 s	Minimum 48 h, maximum 8 days	ASA 100 to 325 mg daily	*At day 14* Composite endpoint of risk of death, MI, and recurrent angina Group A: 16.6% Group B: 19.8% ($p = 0.019$)	*At day 30* Composite endpoint of risk of death, MI, and recurrent angina Group A: 19.8% Group B: 23.3% ($p = 0.02$)
TIMI 11B (1999)[26]	*Group A (1953 patients):* enoxaparin 30 mg IV bolus, followed by 1 mg/kg SC bid *Group B (1957 patients):* unfractionated heparin adjusted to target aPTT of 1.5 to 2.5 times control	Minimum 3 days, maximum 8 days, then enoxaparin SC bid to 43 days (group A) or placebo SC bid to 43 days (group B)	ASA 100 to 325 mg daily	*At day 43* Composite endpoint of death, MI, and urgent revascularization Group A: 17.3% Group B: 19.7% (OR = 0.85, $p = 0.048$)	*At day 8* Composite endpoint of death, MI, and urgent revascularization Group A: 12.4% Group B: 14.5 % (OR = 0.82, $p = 0.048$)

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Table 3. Trials Comparing the Efficacy of Low-Molecular-Weight Heparins in Unstable Angina with Unfractionated Heparin and Acetylsalicylic Acid or Placebo (continued)

Trial	Treatment Groups and No. of Patients	Duration of Treatment	Other Concurrent Medications	Primary Endpoints	Secondary Endpoints
FRISC II (1999)[27]	Group A (1049 patients): dalteparin 120 U/kg SC bid *Group B (1056 patients):* unfractionated heparin adjusted to aPTT	At least 5 days, then *Group A:* dalteparin SC bid or placebo for 3 months *Group B:* no further treatment	ASA 300 to 600 mg initially, then maintenance dose of 75 to 320 mg daily + ß-blocker (+ CCB, organic nitrates if needed)	*At 3 months* Composite endpoint of death and MI Group A: 10.0% Group B: 11.2% (OR = 0.53, p = NS)	*At 6 months* Composite endpoint of death and MI Group A: 13.3% Group B: 13.1% (p = NS)
FRAX.I.S (1999)[28]	*Group A (1166 patients):* nadroparin 86 U/kg IV bolus, followed by 86 U/kg SC bid for 6 days *Group B (1151 patients):* nadroparin 86 U/kg IV bolus, followed by 86 U/kg SC bid for 14 days *Group C (1151 patients):* unfractionated heparin 5000 U bolus + 1250 U/h infusion for 6 days	At least 6 days	ASA 325 mg daily (+ CCB, ß-blocker, nitrates if needed)	*At day 14* Composite endpoint of cardiac death, MI, refractory angina, recurrent unstable angina Group A: 17.8% Group B: 20.0% Group C: 18.0% (p = NS)	*At day 6* Composite endpoint of cardiac death, MI, refractory angina, recurrent unstable angina Group A: 13.8% Group B: 15.8% Group C: 14.9% (p = NS)

ASA = acetylsalicylic acid, aPTT = activated partial thromboplastin time, IUC = units Institute Choay, AMI = acute myocardial infarction, NS = not significant, CCB = calcium-channel blocker, MI = myocardial infarction, RR = relative risk, OR = odds ratio.

ing, and death. Group C, which received both nadroparin and ASA, had significantly fewer events (22% of patients) than the other 2 groups (59% for ASA alone, 63% for ASA and unfractionated heparin, p = 0.00001 between groups A and C and between groups B and C)[18] (Table 3). Acute myocardial infarction occurred in 7% of patients in group A, 6% of those in group B, and none of those in group C; the difference was significant only between groups A and C (p = 0.01). Major bleeding (decrease in hemoglobin of 20 g/L or more, need for transfusion, or both) was found only in the group who received unfractionated heparin (group B); minor bleeding (spontaneous hematoma or bleeding at the puncture sites) occurred in 14% of those in group B and 1.5% of those in group C.

The limitations of this study were its small sample size (smaller than projected) and the lack of double blinding. The sample size was smaller than projected because the study was terminated early, as a result of the significant reduction in ischemic events in group C and significantly higher bleeding complications in group B. The results indicate that nadroparin with ASA was more efficacious than unfractionated heparin with ASA in preventing recurrent angina and appeared to decrease the chance of experiencing myocardial infarction.[18]

A second trial, the Fragmin during Instability in Coronary Artery Disease (FRISC) trial, was conducted in Sweden. It was a prospective, multicentre, randomized, double-blind, parallel-group trial that involved 1506 patients with unstable angina and non-Q wave myocardial infarction.[19] The 746 patients in the active treatment group received dalteparin 120 U/kg SC bid for 6 days, followed by dalteparin 7500 U SC once daily for the next 35 to 45 days. The other 760 patients received placebo injections. All patients received 75 mg of ASA daily along with ß-blockers. Calcium-channel blockers and organic nitrates were added as needed.

The primary endpoint of the study was the rate of death or new myocardial infarction during the first 6 days of treatment. After 6 days of treatment, the dalteparin group had a significantly lower rate of death or myocardial infarction than the placebo group (1.8%

and 4.8%, respectively, $p = 0.001$) (Table 3). In addition, the dalteparin group had less need for intravenous heparin rescue and revascularization. After the 35 to 45 days, treatment was stopped. The original differences between the 2 groups in reduction of death or new myocardial infarction continued. At day 150, however, the rate of death and myocardial infarction in both groups was similar.[19] From this trial it is possible to conclude that dalteparin is better than placebo in preventing subsequent myocardial infarction and death. However, current practice guidelines include both continuous infusion of unfractionated heparin and ASA; therefore, a more relevant assessment of dalteparin's efficacy would require a study comparing unfractionated heparin and dalteparin. This was the goal of the FRIC study.

The Fragmin in Unstable Coronary Artery Disease Study (FRIC) was a prospective, randomized, multinational, parallel-group trial conducted to directly compare the effects of dalteparin and unfractionated heparin in patients with unstable coronary artery disease.[20] A total of 731 patients received dose-adjusted IV unfractionated heparin to obtain an activated partial thromboplastin time of 1.5 times control for 48 h or more, and were then switched to unfractionated heparin (12 500 U SC bid) to complete 6 days of therapy. The other 751 patients received dalteparin 120 U/kg SC bid for 6 days. In the prolonged treatment phase, from day 6 to 45, the dalteparin-treated patients received dalteparin 7500 U SC daily while the patients treated with unfractionated heparin received placebo injections. All patients were started on ASA 75 to 165 mg daily as soon as possible after admission to hospital. Other antianginal medications were administered as per the current practice at each site. The primary endpoints of the study were death, myocardial infarction, and recurrence of angina during days 6 to 45. On day 6, both groups exhibited similar rates of death and myocardial infarction, and equal need for revascularization (relative risk 1.18, 95% confidence interval 0.84 to 1.66) (Table 3).[20] No advantage was observed in continuing once-daily dalteparin 7500 U SC after the sixth day over ASA alone in terms of rate of death and myocardial infarction and need for revascularization (12.3% for both, relative risk 1.01, $p = 0.96$).[20]

The authors suggested that dalteparin is as effective as IV unfractionated heparin in the initial treatment of unstable coronary artery disease, with the benefit of not requiring laboratory monitoring. Unfortunately, the study was not sufficiently powered to detect a difference between the 2 forms of heparin at day 6. One concern with this study was that the unfractionated heparin was titrated to obtain an activated partial thromboplastin time of 1.5 times control values, which is lower than the standard of 1.5 to 2.0 times control values. Therefore, the group receiving unfractionated heparin might have been at a disadvantage. Concerning the primary endpoint of the study, the results indicated that treatment beyond 6 days with dalteparin did not offer any advantage. The authors suggested that the reason for this was that the dalteparin dose was too low in the second phase of the trial to overcome the "hypercoagulable state", as suggested by Théroux and colleagues.[9]

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events (ESSENCE) trial was a randomized, multicentre, double-blind, parallel-group trial that investigated the role of enoxaparin in patients with unstable coronary artery disease.[21] An optimal dose of enoxaparin 1 mg/kg SC bid had been identified in a previous trial (TIMI [Thrombolysis in Myocardial Infarction] 11A).[22] In the ESSENCE trial, a total of 1067 patients received enoxaparin 1 mg/kg SC bid, and 1564 patients received continuous heparin infusion targeted for an activated partial thromboplastin time of 55 to 85 s, for a minimum of 48 h to a maximum of 8 days (Table 3). All of the patients received ASA 100 to 325 mg daily. The primary endpoint of this study was a composite triple endpoint of death, myocardial infarction (or reinfarction), or recurrent angina at 14 days of follow-up. Early in therapy and at day 14, the risk of death, myocardial infarction, or recurrent angina was significantly less in the enoxaparin-treated group than in the continuous-infusion group (16.6% and 19.8%, respectively, $p = 0.019$). The benefit of enoxaparin persisted at day 30 (composite triple endpoint 19.8% and 23.3%, respectively, $p = 0.02$) primarily because of decreased recurrent angina.[21] The need for revascularization at day 30 was significantly lower in the enoxaparin group than in the continuous-infusion group (27.0% and 32.2%, respectively, $p = 0.001$). Only minor bleeding episodes were more frequent in the enoxaparin group; these were associated with ecchymosis at the injection site (18.4% and 14.2%, respectively, $p = 0.001$).

A 1-year follow-up of these patients indicated that the enoxaparin-treated patients continued to have a lower composite endpoint (death, myocardial infarction, or recurrent angina) than the group treated with unfractionated heparin (32.0% and 35.7%, respectively, $p = 0.022$).[23]

The authors attributed the superior effect of enoxaparin in decreasing the number of cardiovascular events (relative to the effects of dalteparin in the FRIC

trial) to enoxaparin's higher ratio of anti-Xa to anti-IIa (Table 1). The role of this ratio is clinically not well understood.

An economic analysis of this trial was performed to determine the cost-effectiveness of enoxaparin compared with unfractionated heparin, with the data from the American arm of the study. Enoxaparin yielded a cumulative cost saving of US$1172 per patient by day 30.[24] The cost saving was associated with eliminating the need for infusion pumps, lower need for laboratory monitoring, fewer percutaneous transluminal angioplasty procedures, fewer diagnostic catherizations, and shorter stays in the intensive care unit.[25] A recent article by Paradiso-Hardy and Oh indicated that in a Canadian hospital setting, the daily costs of SC low-molecular-weight heparin are similar to those of unfractionated heparin when drug acquisition, laboratory, and supply costs are considered.[25]

These initial 4 trials provided evidence that the low-molecular-weight heparin dalteparin could be considered equivalent in efficacy to unfractionated heparin and that only enoxaparin has superior efficacy. However, there were some lingering issues. Was enoxaparin truly superior to unfractionated heparin? What is the optimal treatment length with a low-molecular-weight heparin? In a larger trial, would nadroparin prove statistically superior to unfractionated heparin? Recently, 3 further trials have helped to resolve some of these issues.

The TIMI 11B trial was a prospective randomized, multicentre, double-blind study addressing the question of whether extended use of enoxaparin provided any additional benefit over short-term use.[26] The treatment group consisted of 1953 patients who received enoxaparin 30 mg IV bolus, followed by enoxaparin 1 mg/kg SC bid until hospital discharge or day 8. The other 1957 patients in the study received unfractionated heparin titrated to an activated partial thromboplastin time of 1.5 to 2.5 times control. Patients in the extended treatment arm received enoxaparin until day 43. In this double-blind phase, patients received enoxaparin 40 mg SC bid if they weighed less than 65 kg and 60 mg if they weighed 65 kg or more. The unfractionated heparin group received placebo injections. All patients received ASA 100 to 325 mg daily. The primary endpoint was a composite endpoint of death, recurrent myocardial infarction, or urgent revascularization at day 8 and 43.

At day 8 the enoxaparin group had a statistically significant lower composite endpoint than the unfractionated heparin group (12.4% and 14.5%, respectively, p = 0.048). At day 43 the superiority of enoxaparin continued (17.3% and 19.7%, respectively, p = 0.048). The only concern was that there were more major hemorrhages (overt bleeding resulting in death; hemoglobin drop of 30 g/L or more; retroperitoneal, intracranial, or intraocular bleeding episodes; or requirement for transfusion of 2 or more units of blood) in those who received extended treatment with enoxaparin than in those who received unfractionated heparin (2.9% and 1.5%, respectively, p = 0.021).

The TIMI 11B trial confirmed the superiority of enoxaparin over unfractionated heparin. The extended-treatment phase did not appear to provide any overall therapeutic benefit because of the increase in prevalence of major hemorrhage.

A second trial, Fragmin and Fast Revascularisation during Instability in Coronary Artery Disease (FRISC) II, was a prospective, multicentre, randomized trial to determine the effects of extended anticoagulation with dalteparin.[27] In the initial open phase of the trial, 1049 patients received dalteparin 120 U/kg SC bid for at least 5 days, and 1056 patients received unfractionated heparin adjusted for activated partial thromboplastin time. The patients who had received dalteparin were then randomly assigned into a double-blind extended trial to receive a fixed dose of dalteparin or placebo for 3 months, on the basis of weight and sex. Women weighing less than 80 kg and men weighing less than 70 kg received dalteparin 5000 U SC bid. Women weighing 80 kg or more and men weighing 70 kg or more received dalteparin 7500 U SC bid. All patients received ASA 300 to 600 mg initially, then a maintenance dose of 75 to 320 mg daily.

The primary and secondary endpoints of the study consisted of a composite endpoint of death and myocardial infarction at 3 and 6 months, respectively. There was no statistical difference between dalteparin and unfractionated heparin at either 3 months (10.0% and 11.2%, respectively, p = 0.34) or 6 months (13.3% and 13.1%, respectively, p = 0.93). There was a statistically significant difference between the groups in favour of dalteparin at 1 month, but this difference was not maintained at 3 months. The trial was powered for only the 3- and 6-month endpoints. However, the continued use of dalteparin was associated with a higher risk of major bleeding episodes than in the unfractionated heparin group (3.3% and 1.5%, respectively).

The extended use of dalteparin in FRISC II proved to have superior efficacy in the first month, but this benefit could not be sustained. The authors did a subgroup analysis of their study, which indicated that the patients who did benefit from long-term dalteparin, were those with an increased concentration of troponin T (0.1 µg/L or more).

The final new trial, Fraxiparine in Ischaemic Syndrome (FRAX.I.S.), was a multicentre, prospective, randomized, double-blind, 3-parallel-group trial to determine if nadroparin was beneficial when administered beyond the initial acute treatment period.[28] Two nadroparin groups were compared with a group receiving unfractionated heparin. The 1166 patients in the "nadroparin 6" group received nadroparin 86 U/kg IV bolus followed by 86 U/kg SC bid for 6 days, and the 1151 patients in the "nadroparin 14" group received the same dose of nadroparin but continued the SC injections bid for 14 days. These 2 groups were compared with 1151 patients who received unfractionated heparin adjusted according to the activated thromboplastin time for 6 days (± 2 days). All patients received 325 mg of ASA daily for 3 months.

The primary endpoint of the study was a composite endpoint of cardiac death, myocardial infarction, refractory angina, and recurrence of unstable angina at day 14. The secondary endpoints were the composite endpoint at day 6 and at 3 months. The primary endpoint at day 14 was not statistically significantly different among the 3 groups (Table 3). At day 6, nadroparin was equivalent in efficacy to unfractionated heparin (13.8% and 14.9%, respectively).

These results suggest that nadroparin is equivalent in efficacy to unfractionated heparin, but that there is no advantage to continuing nadroparin beyond the first 6 days of treatment. The results from the FRAX.I.S. trial contrast with those of the initial trial by Gurfinkel and colleagues,[18] which demonstrated a superior effect of nadroparin over unfractionated heparin. The FRAX.I.S. trial was much larger and was double-blinded. Another explanation suggested by the authors was that they ensured that testing of the activated partial thromboplastin time was accurate at each centre and therefore all patients were optimally anticoagulated on unfractionated heparin.

These new findings confirm the superiority of enoxaparin over unfractionated heparin as shown in the ESSENCE trial. They also indicate that both dalteparin and nadroparin are at least as efficacious as unfractionated heparin. Treatment duration still remains unclear, but these initial results indicate that extending the anticoagulation period does not provide any further benefit, but instead could increase the risk of major hemorrhage.

FORMULARY CONSIDERATIONS

The question remains whether these agents should be added to the hospital formulary for acute coronary syndromes. At this time only enoxaparin has shown superior efficacy over unfractionated heparin and would be considered the low-molecular-weight heparin of choice.

Certain restrictions should be applied to the use of low-molecular-weight heparins in hospital. The dosing and absorption of these agents in very obese patients is not known, so for safety reasons, these patients should receive unfractionated heparin. In addition, the literature cautions against the use of low-molecular-weight heparins in people with renal failure. The ESSENCE trial excluded patients who had a creatinine clearance of less than 30 mL/min. Finally, if the need to reverse the anticoagulant effect is foreseen, unfractionated heparin should be used in this patient group, since its effects can be reversed by protamine, whereas there is no effective reversal agent for the anticoagulant effect of low-molecular-weight heparins.

There are still some unresolved issues that need to be addressed regarding the use of low-molecular-weight heparins. It is still unclear why enoxaparin appears to have a superior efficacy over other low-molecular-weight heparins. Some debate exists whether this is attributable to enoxaparin's higher anti-Xa to anti-IIa levels. True superiority of one low-molecular-weight heparin over another would require a trial directly comparing these heparins. Finally, the future of the treatment of acute coronary syndromes will need to include other agents, such as endothelin inhibitors, thromboxane inhibitors, and adhesion molecular inhibitors, to provide additional improvements in outcome over current treatment options.

In summary, low-molecular-weight heparins are becoming the mainstay of treatment in many areas of anticoagulation therapy. With their better side effect profile (compared with unfractionated heparin), the ease of administration, and the reduced need for monitoring activated partial thromboplastin time, they are an attractive alternative to unfractionated heparin. Enoxaparin alone has produced significantly better cardiac outcomes than the standard treatment with unfractionated heparin. The limitations of low-molecular-weight heparins are concerns about reversibility of their anticoagulant effect, unknown absorption in very obese patients, dosing in renal failure, and optimal duration of use.

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