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Scientific Update™

Low molecular weight heparins in the management of acute coronary syndromes

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Intravenous unfractionated heparin plus aspirin has been shown to be more effective than aspirin alone in reducing the risk of death or myocardial infarction (MI) in patients with unstable angina. Low molecular weight heparins (LMWHs) demonstrate improved pharmacological and pharmacokinetic properties relative to standard heparin, and these advantages have translated into similar or even greater clinical efficacy in several large-scale clinical trials evaluating their use. The simple mode of administration and lack of need for anticoagulation monitoring make LMWHs an extremely attractive option in the treatment of patients with acute ischemic coronary syndromes presenting without persistent ST segment elevation.

Pathophysiology of acute coronary syndromes

Disruption of an atherosclerotic plaque, accompanying platelet activation and aggregation, and thrombosis play a fundamental role in the pathogenesis of unstable angina, acute myocardial infarction (MI), and sudden death.[1-3] The rupture of a plaque exposes the subendothelial constituents of the vessel wall, as well as the lipid content of the plaque, to circulating blood elements. This initiates platelet aggregation in the formation of thrombin, as well as vasoconstriction caused by substances released by aggregating platelets and damaged endothelium. These events lead to transient reductions in coronary blood flow. While the vast majority of such acute vascular lesions will resolve with repair of the fissure or erosion, in up to 20% of all episodes of acute plaque disruption, a thrombotic complication will occur in the absence of antithrombotic treatment.

Antithrombotic therapy

Platelet inhibition by aspirin has been a mainstay of treatment, reducing the risk of MI by at least 25%.[4] There is also compelling evidence that treatment with glycoprotein IIb/IIIa receptor antagonists can prevent 1.5 to 2 deaths or non-fatal infarctions that would otherwise occur within 30 days of plaque rupture for every 100 patients treated.[5]

In addition to antiplatelet therapy, thrombus formation can be prevented by direct or indirect inactivation of thrombin or by inhibition of thrombin production by the intrinsic or extrinsic limbs of the coagulation pathway. Since the discovery of heparin in 1916 and its initial therapeutic use by the late 1930s, heparin has been the only rapid-acting anticoagulant in clinical use. Randomized trials have confirmed the effectiveness of heparin in the prevention and treatment of venous thrombosis and pulmonary embolism, the prevention of mural thrombosis after MI and coronary artery rethrombosis after thrombolysis, and in the treatment of patients with MI and unstable angina.

Potential advantages of low molecular weight heparins

When compared to unfractionated heparin, LMWHs demonstrate less binding to plasma proteins, macrophages, and the endothelium. This results in a more predictable anticoagulant response, greater bioavailability, and a longer half-life (Table 1). In addition, LMWHs have a greater anti-Xa:IIa ratio and a more favourable tissue factor pathway inhibitor (TFPI) release profile than unfractionated heparin,

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Table 1: Advantages of low molecular weight over unfractionated heparins

Advantage	Mechanism
More predictable anticoagulant response	Less binding to plasma proteins and to proteins released from activated platelets and endothelial cells
Dose-independent clearance	Less binding to macrophages
Longer half-life	Less binding to macrophages

Adapted from Weitz[6]

leading to more potent antithrombotic action.[6] LMWHs are also clinically attractive because they have a more consistent pattern of clearance and are easy to administer via the subcutaneous route.

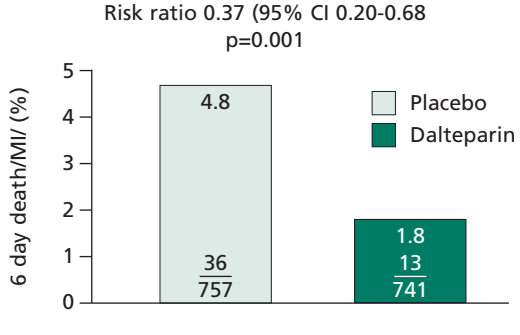
Clinical trials of LMWHs in unstable angina/non-Q-wave MI

Beginning with the first encouraging small open-label trial with nadroparin, conducted by Gurfinkel and colleagues,[7] a series of trials of LMWHs in the management of unstable angina and non-Q-wave MI have been undertaken in the past several years.

FRISC

The landmark Fragmin during Instability in Coronary Artery Disease (FRISC) study demonstrated that dalteparin was superior to placebo for acute-phase management of unstable angina/non-Q-wave MI.[8] This double-blind randomized trial in 1,506 patients compared subcutaneous dalteparin (120 IU/kg twice daily for 6 days, then 7500 IU once daily for the next 35 to 45 days) to placebo injections. All patients received an initial 300 mg of aspirin followed by 75 mg daily. Patients were eligible for study inclusion if they had been admitted to hospital because of chest pain within the previous 72 hours (newly developed, increased, or rest angina) in the setting of ECG changes.

Figure 1: Dalteparin vs placebo for acute-phase management of unstable angina/non-Q-wave MI: The FRISC results



During the first 6 days, the rate of death and new MI was significantly lower in the dalteparin group than in the placebo group (1.8% versus 4.8%; Risk Ratio [RR] 0.37, 95% Confidence Interval [CI] 0.20-0.68; Figure 1). Similarly, the frequency of need for intravenous heparin (3.8% vs. 7.7%; RR 0.49, 95% CI, 0.32-0.75) and need for revascularization (0.4% vs. 1.2%; RR 0.33, 95% CI, 0.10-1.10) was lower among dalteparin-treated patients. The significantly lower death/MI rate represented the first large-scale trial evidence of the benefit of heparin (in this case, a LMWH), in addition to aspirin, in the treatment of unstable angina/non-Q-wave MI patients.

At 40 days, the differences in rates of death and MI and a composite end point (death, MI, or revascularization) persisted, although subgroup analysis showed that the effect was confined to nonsmokers (80% of sample). If interventional procedures done for reasons other than incapacitating symptoms were excluded, there remained a significant reduction in the composite end point. However, 4 to 5 months after the end of treatment, there were no significant differences in the rates of death, new MI, or revascularization.

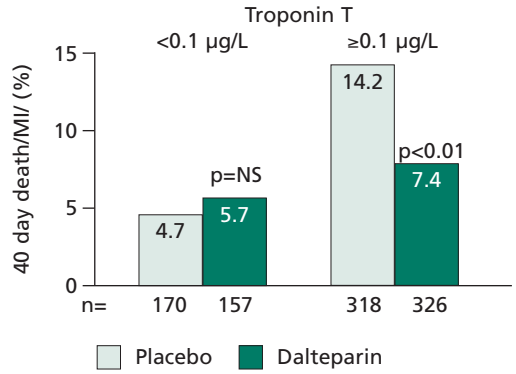
During the acute phase, there were very few major bleeding episodes, and no differences between the treatment groups. Minor bleeding, mainly subcutaneous hematoma at injection sites, was more common in the dalteparin than the placebo group, especially during the acute phase. There were no differences in mean hemoglobin or platelet count between the groups.

FRIC

The Fragmin in Unstable Coronary Artery Disease (FRIC) study[9] was a randomized comparison in 1,482 patients with unstable angina or non-Q-wave MI. All patients received 75 to 160 mg of aspirin daily. In addition, patients were treated with either dose-adjusted intravenous unfractionated heparin or twice-daily weight-adjusted subcutaneous injections of dalteparin (120 IU/kg) in an open-label fashion. In the prolonged treatment phase (days 6 to 45), patients received subcutaneous dalteparin (7500 IU once daily) or placebo in a double-blind fashion.

During the first 6 days, the rate of death, MI or recurrence of angina was 7.5% in the unfractionated heparin-treated patients and 9.3% in the dalteparin-treated patients (relative risk 1.18; 95% CI, 0.84-1.66). Between days 6 and

Figure 2: Dalteparin vs placebo in patients with and without elevated troponin T levels



45, the composite end point was 12.3% in both the placebo and dalteparin groups.

ESSENCE

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) study[10] demonstrated a significant advantage with another LMWH, enoxaparin, as compared with unfractionated heparin for 14-day risk of death, MI, or recurrent angina (16.6% versus 19.8%, p=0.019). It has been hypothesized that the reason that the ESSENCE, but not the FRIC study, showed an advantage over unfractionated heparin may relate to:

- differences in the anti-Xa:IIa activities (approximately 3:1 with enoxaparin vs. 2:1 with dalteparin), and/or
- the smaller sample size in the FRIC study
- differences in the time window for enrollment: FRIC ≤72 hours; ESSENCE ≤24 hours.
- differences in the average duration of therapy: FRIC = 6 days; ESSENCE = 2.6 days

Indeed, FRIC may have been underpowered to detect the difference between two active treatments, even if a true benefit of dalteparin did exist over unfractionated heparin.

TIMI 11B

The TIMI 11B study was also presented at the XXth Congress. For this study, 3,910 patients with unstable angina/non-Q-wave MI were randomized. The 14-day composite end point (death, MI, urgent revascularization) was significantly lower among enoxaparin-treated compared to unfractionated heparin-treated patients (14.2% versus 16.6%, respectively, p=0.03). This benefit was maintained at day 43 (17.3% versus 19.6%, respectively, p=0.049), but there was no additional benefit gained by continuing subcutaneous enoxaparin administration on an outpatient basis.[11] However, the primary end-point of the chronic phase showed no incremental benefit beyond the acute phase. Of note, only 60% of patients enrolled in the acute phase continued on to the chronic phase.

FRAX.I.S.

The FRAX.I.S. study was also presented at the XXth Congress meeting and was a 3,460 patient study in unstable angina/non-Q MI.[12] This randomized, double-blind trial had three treatment groups:

- Group 1 received unfractionated heparin for 6±2 days;
- Group 2 received nadroparin (IV bolus then subcutaneous BID) for 6±2 days;
- Group 3 received nadroparin (IV bolus then subcutaneous BID) for 14 days.

All patients received up to 325 mg daily of aspirin. There were no differences between the treatment groups with respect to the composite end point (death, MI, refractory or recurrent angina) at 6 days (14.9% vs. 13.8% vs. 15.8%) or 14 days (18.1% vs. 17.8% vs. 20%). At 3 months time, there was a higher endpoint rate in patients who had received 14 days of nadroparin therapy (Group 3, 26.2% vs. unfractionated heparin, 22.2%, p<0.05).

Troponin T in FRISC: Identification of patients who benefit from dalteparin

In an interesting substudy from the FRISC trial, Lindahl et al followed a group of patients (n=971) who underwent troponin T blood sampling at the time of study inclusion.[13] As seen in Figure 2, patients with elevated troponin T levels (indicating myocardial necrosis and those at higher risk for subsequent events), experienced a significant benefit from dalteparin as compared to placebo at 40-day follow-up. Dalteparin reduced the incidence of death or MI at 6 days from 6% to 2.5% (p<0.05) and at 40 days from 14.2% to 7.4% (p<0.05) in 644 patients with troponin T levels ≥0.1 µg/L. In contrast, among the 327 patients with troponin T levels <0.1 µg/L, there was a modest insignificant reduction among dalteparin-treated patients at 6 days: 2.4% placebo vs. 0% dalteparin, p=0.12. At 40 days, the death/MI rates were similar among the placebo and dalteparin groups with initial troponin T level <0.1 µg/L (4.7% vs. 5.7%, respectively). Thus, elevation of troponin T identified a subgroup of patients in whom treatment with subcutaneous dalteparin was superior to aspirin alone. This simple cardiac marker could help physicians decide which patients may benefit the most from LMWH administration.

Future applications of LMWH in acute coronary syndromes

Given the benefit seen with LMWH use in unstable angina/non-Q-wave MI, the future application of this therapy

in acute coronary syndromes may be as an adjunct to thrombolysis. The Fragmin in Acute Myocardial Infarction (FRAMI) study[14] enrolled 776 patients in a double-blind comparison of dalteparin (150 IU/kg subcutaneously BID during the hospital period) and placebo. Thrombolytic therapy and aspirin were administered to 92% and 98% of patients, respectively. A primary composite end point of thrombus formation diagnosed by echocardiography and arterial embolism on day 9±2 was significantly lower among dalteparin-treated patients (14.2% versus 21.9%, p=0.03). Since only 1 patient in the dalteparin and none in the placebo group experienced arterial embolism, this benefit was mainly related to decreased left ventricular thrombus formation. Dalteparin was associated with an increased risk of major (2.9% vs. 0.3%, p=0.006) and minor hemorrhage (14.8% vs. 1.8%, p<0.001), and this may relate to the use of a higher dose of dalteparin than was administered in either the FRISC or FRIC studies, particularly following thrombolytic therapy.

FRISC-II

While antiplatelet and antithrombotic therapy, including LMWH, have resulted in a decrease in short-term events in unstable angina/non-Q-wave MI patients, 10% to 15% of patients will die or develop MI, and another 35% to 50% will require coronary revascularization procedures over the next 6 to 12 months time. The FRISC-II trial is a prospective, multi-centre, randomized study comparing the efficacy of 3 months' continuation of subcutaneous treatment with dalteparin with that of placebo. In addition, this study will compare a direct invasive strategy (coronary angiography ± revascularization will be scheduled within 7 days after admission) with a stepwise selective approach (angiography ± revascularization is only performed in patients with refractory or recurrent symptoms or with severe ischemia on a symptom-limited predischarge exercise test). Over 3,000 patients have been recruited in 65 to 70 Scandinavian centres and it is anticipated that the results will be presented in March, 1999.[15]

Conclusion

The LMWHs are clearly easier to administer than unfractionated heparin, are of at least equivalent efficacy in treating patients with unstable angina or non-Q-wave MI, and may also play a role as an adjunct to thrombolytic-treated MI as further information from clinical trials becomes available. The FRISC II study will further elucidate the use of LMWH in patients being treated by either a direct invasive or stepwise selective approach to post-unstable angina/non-Q-wave MI risk stratification.

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