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Scientific Update™

Low Molecular Weight Heparin: Management Strategies in Acute Coronary Syndromes

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The acute coronary syndromes (ACS) of myocardial infarction (MI) and unstable angina are increasingly important causes of morbidity and mortality. Rupture of an atherosclerotic plaque and subsequent thrombus formation is the underlying precipitant of most ACS. Consequently, the early treatment of the patient with an ACS is directed towards removal of occlusive thrombus and prevention of further thrombosis. As both platelet aggregation and activation of the coagulation system play a pivotal role in thrombosis, it is essential to target treatment to both components. Aspirin (ASA), clopidogrel, and the glycoprotein (GP) IIb/IIIa receptor inhibitors eptifibatide and tirofiban are antiplatelet agents effective in reducing adverse outcomes in a wide range of ACS. The addition of heparin to ASA reduces death and MI by a further 33%[1] to 63%[2] on top of the benefits of ASA alone. However, unfractionated heparin is far from the ideal agent to inhibit coagulation. The anticoagulant response of unfractionated heparin is unpredictable and fewer than 50% of patients are within the therapeutic range after 24 hours treatment.[3] Furthermore, there is a narrow therapeutic window, with bleeding associated with excessive anticoagulation and arterial occlusion occurring more frequently in patients not adequately anticoagulated. Unfractionated heparin may increase platelet aggregation and be associated with rebound thrombosis and myocardial ischemia on discontinuation of the infusion.[4] In contrast, the low molecular weight heparins (LMWHs) result in immediate and predictable anticoagulation and can be administered as twice-daily subcutaneous injections. Although not generalizable to all LMWHs, the discontinuation of enoxaparin in the ESSENCE trial was not associated with rebound ischemia.[5]

Unfractionated heparin, in combination with other treatment modalities, has been shown to be of proven benefit in the management of a range of ACSs (Table 1). Until recently, the use of LMWHs was confined to the management of ACSs without ST segment elevation on ECG. Now, increasing evidence points to the benefits of using LMWHs for the complete spectrum of ACS. In the future, it is predicted that the LMWHs will become the standard of care for all ACSs.[6]

Non-ST segment elevation acute coronary syndromes

A recently published meta-analysis[7] suggested that when the LMWHs are compared to unfractionated heparin in non-ST segment elevation ACS (NSTE ACS), the outcomes of the two treatments are identical. Yet, when the trials that directly compare a LMWH with unfractionated heparin are examined, only enoxaparin is superior to unfractionated heparin (Figure 1). In both the ESSENCE[8] and TIMI 11B[3] studies, enoxaparin resulted in a consistent treatment benefit that was maintained for one year following treatment.[9] Hence, the validity of lumping the different LMWHs into a meta-analysis and assuming a class-effect is questionable.

The enhanced benefits of enoxaparin beyond those of unfractionated heparin are seen in higher risk patients with high TIMI risk scores[10] and with positive troponin I.[11] Scien-

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Table 1: Heparin usage in acute coronary syndromes

- *Non-ST segment elevation ACS:*
  With ASA, clopidogrel, GP IIb/IIIa inhibitors
- *ST segment elevation ACS:*
  With thrombolysis using tPA
- *Peri- percutaneous coronary intervention for ACS*
  With or without GP IIb/IIIa inhibitor

tific plausibility for the clinical benefits of enoxaparin beyond those of other LMWHs is based on these properties:

- more prolonged inhibition of factor Xa relative to thrombin[12]
- greater release of tissue factor inhibitor[13]
- less release of von Willebrand factor[14]

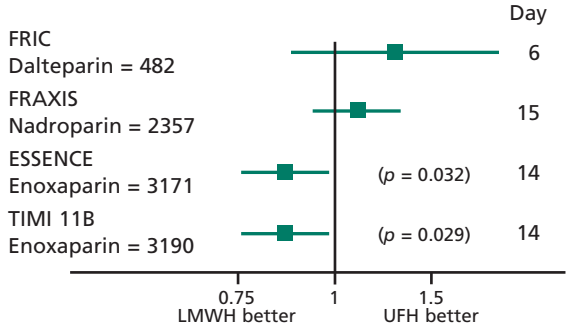
Furthermore, enoxaparin was shown to be consistently superior to unfractionated heparin whatever the level of anticoagulation achieved with the unfractionated heparin.[15]

LMWHs, especially enoxaparin, are gradually becoming the standard of care for the management of patients with NSTE ACS. The Canadian ACS Registry (unpublished data) shows that 30%-40% of NSTE ACS patients currently receive LMWH, whereas European utilization is greater than 50%.[16]

Combining of LMWH and GP IIb/IIIa inhibitors in non-ST elevation ACS

The GP IIb/IIIa inhibitors play an important role in the management of the NSTE ACS patient with high-risk features (eg, ST depression >1-2 mm, positive biomarkers, heart failure, and hypotension). As most of these high-risk patients will undergo early coronary angiography and revascularization, any treatment algorithm incorporating LMWHs must consider the impact of treatment on percutaneous coronary intervention (PCI) and coronary bypass surgery. Unfractionated heparin was combined with GP IIb/IIIa inhibition in the PRISM Plus trial[17] (tirofiban) and in the PURSUIT trial[18] (eptifibatide), and was considered to play an important role in achieving the treatment benefit of the two agents. As yet, there are limited data to show the safety and efficacy of combining a GP IIb/IIIa inhibitor with LMWH.

Figure 1: Comparison of LMWHs with unfractionated heparin on death/MI and the need for urgent revascularization in the management of non-ST segment elevation ACS



The studies described in Table 2 suggest that the combination of a GP IIb/IIIa inhibitor and a LMWH is not associated with an excessive rate of major hemorrhage, and has a similar safety profile as when a GP IIb/IIIa inhibitor is used with unfractionated heparin. The combination of the GP IIb/IIIa inhibitor with a LMWH appears to be safe whether or not the patient subsequently undergoes cardiac catheterization or revascularization. With the results of A to Z, INTERACT and NICE 5, we should have adequate efficacy and safety data to show whether a LMWH is the heparin of choice to combine with a GP IIb/IIIa inhibitor.

LMWHs: Interaction with percutaneous coronary intervention

In North America, there has been a reluctance to use LMWHs in patients with non-ST segment elevation ACS because of the high rates of cardiac catheterization and PCI in this group of patients. Cardiologists are concerned about whether LMWHs can be combined with the GP IIb/IIIa inhibitors and how to manage anticoagulation in the catheter laboratory in patients who have received LMWHs. Several trials have demonstrated the successful use of LMWHs prior to and during coronary angiography and PCI.[24-26]

The NICE 1 and 4 studies[27] examined the use of enoxaparin with or without abciximab in patients undergoing percutaneous intervention. These studies showed that enoxaparin was a safe alternative for anticoagulation whether or not abciximab was given. The NICE 3 study[21] has demonstrated the safety of combined enoxaparin and GP IIb/IIIa antagonists in medically-treated patients whether or not they proceed to cardiac catheterization. In the 645 patients given enoxaparin and a GP IIb/IIIa antagonist (abciximab (145), eptifibatide (272), and tirofiban (228)) the non-CABG major bleeding rate was 1.9% which is similar to the 2% rate observed in historical controls. The NICE 1, 3, and 4 studies provide us with safety data that increase our confidence in using LMWHs in the treatment of a wide spectrum of patients with ACS. Interventional cardiologists are also becoming accustomed to LMWHs use both before and during the procedure. As they become less dependent on higher levels of heparinization, and GP IIb/IIIa inhibitors utilization increases, the application of LMWHs in the catheterization laboratory will likely become more frequent.

Table 2: Combination of LMWH and GP IIb/IIIa inhibitor in the management of non-ST segment elevation ACS				
Study	**Agents**		***n***	**Outcome endpoint**
	GP IIb/IIIa	**LMWH**		
ACUTE 1[19]	Tirofiban	Enoxaparin	53	Equivalent safety endpoints
ACUTE 2[20]	Tirofiban	Enoxaparin	525	Bleeding similar between UFH (0.5%) and LMWH (0.6%)
NICE 3[21]	abciximab, tirofiban and controls on UFH	Enoxaparin	661	Bleeding rates (1.9%) with LMWH similar to historical eptifibatide
PARAGON B[22]	Lamifiban	Any LMWH not randomized	2586	Similar major bleeding LMWH 1.5%, UFH 1.6%
GUSTO IV[23]	Abciximab	Dalteparin	974	Major bleeding Dalteparin 1.3%, UFH 0.7% NS
A to Z	Tirofiban	Enoxaparin	5200	Reports 2001: Composite efficacy / safety
INTERACT	Eptifibatide	Enoxaparin	720	Reports 2001: Safety, ST segment changes
NICE 5	Any GP IIb/IIIa	Enoxaparin	8000	Reports 2002: Death / MI

LMWHs: Combination with thrombolytic therapy in ST segment elevation ACS

Prevention of rethrombosis with heparin plays an important role after thrombolytic therapy with tPA and its analogues. Successful maintenance of arterial patency depends on adequate levels of anticoagulation. However, excessive anticoagulation with unfractionated heparin has been associated with early cardiac mortality and excessive bleeding. Unfortunately, unfractionated heparin, given as a bolus injection and followed by IV injection, rarely achieves target aPTT levels in the first 24 hours. LMWH after thrombolysis would provide more reliable and stable anticoagulation, which should translate into maintained coronary patency and reduced recurrent ischemic events. Previous small studies have suggested that compared to placebo, LMWHs added to thrombolytic therapy with streptokinase result in excellent patency of the coronary artery, less recurrent ischemia, and infarction without excessive bleeding complications.[28,29] The ASSENT-PLUS study[30] also demonstrated a trend toward better reperfusion in patients thrombolysed with r-tPA and dalteparin compared to unfractionated heparin. The HART 2 study included 400 patients treated with front loaded tPA and aspirin who were randomized to unfractionated heparin or enoxaparin. Patency at 90 minutes showed a trend in favour of enoxaparin (TIMI 2/3 flow at 90 minutes UFH 75.1%, enoxaparin 80.1%) as well as a trend in favour of less reocclusion (Patients with initial TIMI 3 flow: reocclusion rates: UFH 9.1%, enoxaparin 3.1%). Rates of intracranial hemorrhage, major hemorrhage and transfusion needs were similar in the two treatment groups.

The AMI-SK trial (presented at the 50th Annual Scientific Sessions of the American College of Cardiology in March 2001) showed that enoxaparin added to streptokinase improves TIMI 3 flow, ST segment resolution, and reduces clinical events without any increase in major bleeding. The placebo controlled trial added enoxaparin as a 30 mg bolus, followed by subcutaneous injection of enoxaparin 1 mg/kg every 12 hours for 5 days. Enoxaparin improved TIMI 2 and 3 flow at 5-10 days after the acute event, and ST segment resolution at 90 and 180 minutes (Table 3).

In addition, the composite endpoint of death, reinfarction, and recurrent angina at 30 days after treatment was reduced from 21% to 13.4% $p=0.03$). These benefits of enoxaparin were achieved with no significant increase in major bleeding rates (placebo 2.8%, enoxaparin 4.8% $p=0.2$).

Therefore, the addition of a LMWH to thrombolytic treatment with streptokinase appears to result in more rapid reperfusion and better-sustained patency of the culprit artery. Whether these benefits will translate into reduced 30-day mortality rates that are comparable to those achieved with tPA is unknown. Yet, these promising results indicate the

Table 3: Angiographic and ECG ST segment outcomes of AMI-SK trial			
TIMI flow at 5-10 days	**Placebo *n*=187**	Enoxaparin ***n*=202**	***p***
TIMI 3 flow	57.8%	70.3%	<0.001
TIMI 2/3 flow	71.7%	87.6%	<0.001
Complete ST segment resolution			
90 minutes	11.1%	15.7%	0.012
180 minutes	25.4%	35.3%	<0.004

need for a larger scale clinical trial. Currently, no adequate data are available to show a clear improvement in outcomes and reduced hemorrhagic complications to justify using LMWHs rather than unfractionated heparin with tPA. Further information will be forthcoming from the ASSENT-3 study, yet other large clinical trials are necessary to confirm the advantages of LMWHs after thrombolysis.

Conclusions

• LMWHs are at least as effective as unfractionated heparin in the prevention of death/MI and recurrent ischemia in patients with non-ST segment elevation ACSs.

• Enoxaparin has been shown in two clinical trials to be superior to unfractionated heparin in the early management of non-ST segment elevation ACS resulting a sustained benefit up to one year after the acute event.

• Higher risk patients (high TIMI risk score and/or positive troponin) have a greater benefit when given enoxaparin rather than unfractionated heparin.

• Patients can safely receive an intravenous GP IIb/IIIa inhibitor while also receiving LMWH without any excess of hemorrhagic complications. As yet, there are no adequate data to compare the efficacy of the two regimens.

• Percutaneous coronary intervention can be safely performed in patients receiving a LMWH, with or without a GP IIb/IIIa inhibitor.

• Preliminary studies suggest that LMWHs used after thrombolysis can improve early reperfusion, and prevent recurrent ischemic episodes. However, larger scale clinical trials are necessary before the efficacy and safety of LMWHs are sufficiently proven to warrant a change from unfractionated heparin to a LMWH such as enoxaparin.

• It is likely that the LMWHs, especially enoxaparin, will be more widely used across the spectrum of acute coronary syndromes, and gradually replace the use of unfractionated heparin.

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