Optimizing Adjunctive Antithrombotic Therapy in the Treatment of Acute Myocardial Infarction: A Role for Low-Molecular-Weight Heparin

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Summary: Thrombotic complications account for a large proportion of in-hospital deaths from acute myocardial infarction (MI). Although thrombolytic therapy has greatly improved clinical outcomes following MI, thrombin released during clot lysis has a prothrombotic effect, and the thrombolytic agents themselves may directly activate platelets. Antithrombotic therapy as an adjunct to thrombolysis improves the speed and extent of artery recanalization and reduces the incidence of secondary ischemic complications. The current treatment standard is unfractionated heparin (UFH) administered intravenously for 24–48 h. However, UFH has not been unequivocally shown to improve outcomes in large-scale, randomized clinical trials, and shows no evidence of benefit when used as an adjunct to streptokinase-based thrombolysis. Unfractionated heparin also has several clinical and practical disadvantages, such as the need for coagulation monitoring, difficulties attaining a stable and reliable anticoagulant effect, and the risk of hemorrhagic side effects. Low-molecular-weight heparin (LMWH) represents a safe and effective alternative antithrombotic therapy, with a stable and predictable anticoagulant effect, potential for use in combination with either fibrin-specific or streptokinase-based thrombolysis. Unfractionated heparin also represents a safe and effective alternative antithrombotic therapy. Several randomized clinical trials have shown that adjunctive LMWH is at least as effective as UFH in the acute phase of MI, is associated with fewer in-hospital recurrent ischemic events, and has an acceptable safety profile.

Key words: acute myocardial infarction, thrombolysis, antithrombotic therapy, unfractionated heparin, low-molecular-weight heparin, enoxaparin

Introduction

Despite advances in the early management of ST-segment elevation myocardial infarction (STEMI), mortality and morbidity in these patients remain high. Although arrhythmic consequences of left ventricular dysfunction account for some of these events, a significant proportion are caused by thrombotic complications which result from an increase in thrombin activity after an infarction. Paradoxically, thrombolytic drugs, which are given to hasten dissolution of the culprit coronary occlusive thrombus, may themselves contribute to this augmented thrombin activity. Although thrombolytic therapy has demonstrated unequivocal benefit in the treatment of STEMI, these agents directly activate platelets. In addition, clot lysis during thrombolytic therapy releases a pool of trapped, clot-bound thrombin, which is then available for continued thrombus propagation. Clinical outcomes after thrombolysis are largely governed by the speed and extent of restoration of patency to the infarcted artery and the prevention of secondary ischemic complications, such as reinfarction due to secondary thrombosis. Early management therefore involves a multifaceted approach comprising a thrombolytic, an antiplatelet, and an antithrombin agent.

Recent advances in thrombolytic therapy, such as bioengineered variants of the tissue plasminogen activator (re-teplase, tenecteplase), which can be administered as bolus regimens, have simplified the management of STEMI, facilitated early treatment, and have been adopted rapidly into the standard of care. In contrast, there has been little change in the antithrombotic component of adjunctive therapy, and unfractionated heparin (UFH) is still the most widely used agent worldwide. In this review, emerging data concerning the use of low-molecular-weight heparin (LMWH) as an alternative to UFH will be presented, highlighting the clinical and practical advantages of this newer therapy.
Antithrombotic Therapy in ST-Segment Elevation MI

Unfractionated Heparin

Current guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) and the Taskforce of the European Society of Cardiology for the management of patients with STEMI recommend that UFH be started concurrently with thrombolytic therapy and continued for at least 48 h.\(^1,2\) It is important to note that, despite the consistency of these recommendations, the underlying evidence for them comes only from small studies with angiographic endpoints that demonstrated improved outcomes with intravenous UFH.\(^3-11\) There are no unequivocal data from large, randomized clinical trials confirming the benefits of UFH over placebo as adjunctive therapy to thrombolytic agents. In the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico (GISSI) 2 study and the Third International Study of Infarct Survival (ISIS-3), subcutaneous UFH plus tissue plasminogen activator (t-PA) conferred no mortality advantage over t-PA alone.\(^3,17\) In the Global Use of Strategies To open Occluded coronary arteries (GUSTO) trial, the best outcomes were observed in patients receiving accelerated t-PA plus intravenous UFH, but no patient group received the same regimen of t-PA alone,\(^5\) therefore it is not possible to determine whether the benefit of accelerated t-PA was increased by, or independent of, concomitant UFH.

Neither the ISIS-3 nor the GISSI-2 study demonstrated improved outcomes using streptokinase plus subcutaneous UFH compared with streptokinase alone.\(^3,17\) Thus, there is no compelling evidence for the use of UFH in conjunction with streptokinase-based regimens.\(^11\)

Unfractionated heparin has several practical disadvantages. Patients receiving intravenous UFH require frequent coagulation monitoring because of its unpredictable anticoagulant effect. Even with dose adjustment to maintain appropriate activated partial thromboplastin times (aPTTs), consistent levels of anticoagulation are difficult to achieve. In the GUSTO I and Thrombolysis in Myocardial Infarction (TIMI) 9B studies, approximately half the UFH-treated patients had aPTTs below the target level.\(^18,19\) This is particularly important, given that improved patency was closely tied to adequate anticoagulation in earlier angiographic studies of adjunctive UFH.\(^3,14\) Treatment with UFH also carries a significant risk of hemorrhagic complications, in view of which the ACC/AHA guidelines recommend weight-adjusted dosing.\(^12\) The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 (ASSENT-3) trial, which used the recommended weight-adjusted dose of UFH, reported fewer major bleeding complications and a lower rate of blood transfusions than the ASSENT-2 trial, which used a less fully weight-adjusted UFH dose.\(^20,21\) Other heparin-related side effects include heparin-induced thrombocytopenia, osteoporosis, and local heparin-related skin allergy.\(^22,23\)

Theoretical Advantages of LMWH

Following administration, LMWH is cleared by the reticuloendothelial system less avidly than UFH, and binds less strongly to circulating plasma proteins,\(^24,25\) resulting in a longer half-life and more stable levels of anticoagulation. Furthermore, LMWH results in greater inhibition of thrombin generation (higher anti-factor Xa:anti-factor IIa ratio) and prolonged anti-factor Xa activity (Table I). Additional advantages of LMWH over UFH include greater inhibition of von Willebrand factor and less platelet activation, resulting in a greater net antplatelet effect than UFH.\(^24,26\) Unlike UFH, patients receiving LMWH do not require coagulation monitoring.\(^24\) In addition, LMWH is administered as convenient subcutaneous injections, either once or twice daily.

There is now considerable experience with several LMWHs in the management of acute coronary syndromes (ACS), in which a combined antiplatelet and anticoagulant regimen is also the recommended approach.\(^27\) In ACS, the LMWH enoxaparin has consistently shown sustained improvements in ischemic outcomes compared with UFH\(^24-30\) and is less likely than UFH to induce rebound ischemia.\(^31\)

LMWH as an Adjunct to Streptokinase

Although large randomized clinical trials have failed to demonstrate any clinical benefits with subcutaneous UFH as an adjunct to streptokinase-based thrombolysis, LMWH has shown clinical potential in this setting (Table II).\(^32-35\)

The randomized, double-blind, placebo-controlled Biochemical Markers in Acute Coronary Syndromes (BIOMACS II) trial evaluated dalteparin as an adjunct to streptokinase and aspirin in 101 patients with STEMI.\(^35\) Dalteparin showed a nonsignificant trend toward higher rates of TIMI flow grade 3 in infarcted arteries (68% with dalteparin vs. 51% with placebo, p = 0.10), and a lower incidence of recurrent ischemia (16 vs. 38%, p = 0.04).

In the placebo-controlled Fragmin in Acute Myocardial Infarction (FRAMI) trial of dalteparin as an adjunct to streptokinase (n = 776), dalteparin significantly reduced the incidence of left ventricular thrombus formation in patients with acute anterior myocardial infarction.\(^33\) Dalteparin was associated with higher bleeding rates than placebo (2.9 vs. 0.3%).

The placebo-controlled Acute Myocardial Infarction-Streptokinase (AMI-SK) study (496 patients) evaluated enoxaparin for 3–8 days in conjunction with streptokinase.\(^34\) Enoxaparin therapy significantly improved arterial patency (70 vs. 58%, p = 0.01) and significantly reduced the incidence of the composite 30-day triple endpoint of death, reinfarction, and recurrent angina (13 vs. 21%, p = 0.03). These improvements in clinical outcomes were attained at the expense of a nonsignificant increase in the rate of major hemorrhage (4.8 vs. 2.5%, p = 0.2).

Recently, enoxaparin has been directly compared with UFH in 300 patients receiving thrombolytic therapy (mostly streptokinase). Antithrombin treatment was given for 4 days, and the primary combined endpoint (death, nonfatal reinfarction, or readmission for unstable angina) was assessed at 90 days.\(^32\) Enoxaparin reduced the rate of the combined endpoint (26 vs. 36%, p = 0.04) without an excess in the rate of major hemorrhage (3 vs. 4% for enoxaparin and UFH, respectively). There was evidence to suggest that the incidence of rebound clinical events was re-
TABLE I  The advantages and limitations of antithrombotic therapy with low-molecular-weight heparin compared with unfractionated heparin

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Limitation</th>
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<tbody>
<tr>
<td><strong>Pharmacologic</strong></td>
<td></td>
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<tr>
<td>Higher anti-Xa:anti-IIa ratio</td>
<td>Antithrombotic effect cannot be “stopped” immediately, in case of emergency, e.g., immediate surgical intervention required</td>
</tr>
<tr>
<td>High bioavailability (~90%)</td>
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<tr>
<td>Longer half-life (2–4 times UFH)</td>
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<tr>
<td>Prolonged anti-Xa activity</td>
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<tr>
<td>Greater inhibition of von Willebrand factor (level differs between the LMWHs)</td>
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<tr>
<td>Less platelet activation</td>
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<tr>
<td>Resistance to inactivation by platelet factor 4</td>
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<tr>
<td><strong>Clinical</strong></td>
<td></td>
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<tr>
<td>Effective with both streptokinase-based and fibrin-specific thrombolysis</td>
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<tr>
<td>Less recurrent ischemia or infarction</td>
<td></td>
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<tr>
<td>Fewer heparin-related side effects (e.g., HIT, local skin reactions)</td>
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<tr>
<td>No need for coagulation monitoring</td>
<td></td>
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<tr>
<td><strong>Practical</strong></td>
<td></td>
</tr>
<tr>
<td>Convenient once- or twice-daily injections</td>
<td>More expensive</td>
</tr>
<tr>
<td>Cost effective</td>
<td></td>
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</tbody>
</table>

Abbreviations: HIT = heparin-induced thrombocytopenia, LMWH = low-molecular-weight heparin, UFH = unfractionated heparin.

TABLE II  Summary of clinical trials of low-molecular-weight heparin as an adjunct to streptokinase-based thrombolysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>LMWH</th>
<th>Comparator</th>
<th>Patients (n)</th>
<th>Efficacy outcomes</th>
<th>Safety outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIOMACS II</td>
<td>Dalteparin</td>
<td>Placebo</td>
<td>101</td>
<td>Rate of TIMI 3 flow: 68% with dalteparin vs. 51% with placebo (p = 0.10)</td>
<td>No cerebral bleeds</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rate of recurrent ischemic episodes at 6–24 h: 16% with dalteparin vs. 38% with placebo (p = 0.04)</td>
<td>Incidence of hemorrhage higher in dalteparin group (5/6 events, 2 major bleeds)</td>
</tr>
<tr>
<td>FRAMI</td>
<td>Dalteparin</td>
<td>Placebo</td>
<td>776 (517 evaluable)</td>
<td>Incidence of thrombus/embolism: 14.2% with dalteparin vs. 21.9% with placebo (p = 0.03)</td>
<td>Incidence of major hemorrhage: 2.9% with dalteparin vs. 0.3% with placebo (p = 0.006)</td>
</tr>
<tr>
<td>AMI-SK</td>
<td>Enoxaparin</td>
<td>Placebo</td>
<td>496</td>
<td>Rate of TIMI 3 flow: 70% with enoxaparin vs. 58% with placebo (p = 0.01)</td>
<td>Incidence of major hemorrhage at 30 days: 4.8% with enoxaparin vs. 2.5% with placebo (p = 0.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Triple endpoint (death, reinfarction, and recurrent angina) at 0 days: 13% with enoxaparin vs. 21% with placebo (p = 0.03)</td>
<td></td>
</tr>
<tr>
<td>Baird et al.</td>
<td>Enoxaparin</td>
<td>UFH</td>
<td>300</td>
<td>Incidence of 90-day composite end-point (death, nonfatal reinfarction, or admission for UA): 36% with UFH vs. 26% with enoxaparin (p = 0.04)</td>
<td>Incidence of major hemorrhage: 4% with UFH vs. 3% with enoxaparin</td>
</tr>
</tbody>
</table>

Abbreviations: TIMI flow = Thrombolysis in Myocardial Infarction flow (grades 0–3), UA = unstable angina, BIOMACS = BIOchemical Markers in Acute Coronary Syndrome, FRAMI = FRagmin in Acute Myocardial Infarction, AMI-SK = Acute Myocardial Infarction-Streptokinase. Other abbreviations as in Table I.

Reduced by enoxaparin: the rate of reinfarction from Days 4–6 was 6.6% with UFH but only 2.2% with enoxaparin (p = 0.05).

In the smaller trials of LMWH with streptokinase, a reduction in the incidence of reinfarction and/or recurrent ischemia was consistently observed. Recently, the Hirulog and Early Reperfusion or Occlusion (HERO-2) study demonstrated that, in patients receiving streptokinase, the direct antithrombin agent bivalirudin reduced rates of reinfarction compared with UFH.36
However, this benefit was achieved with a significant financial cost and a small incremental risk of bleeding. The average cost of bivalirudin is currently more than US $400 per dose, therefore the combined cost of bivalirudin and streptokinase approaches that of the recombinant fibrinolytic drugs, thus removing the major incentive for the use of streptokinase. When compared with the direct thrombin inhibitors, the ease of use and modest cost of LMWH renders the latter more attractive in less affluent countries where streptokinase is the most widely used thrombolytic drug. Therefore, if the promising data from the phase 2 trials were to be confirmed in large-scale studies, the combination of streptokinase with LMWH could have global application and therefore a major impact on outcomes following ST-segment elevation myocardial infarction (STEMI).

LMWH as an Adjunct to Fibrin-Specific Thrombolysis

Table III summarizes the clinical experience to date with LMWH in combination with fibrin-specific thrombolytic agents. The feasibility of LMWH therapy was established in the small-scale Fraxiparin Anticoagulant Therapy in Myocardial Infarction Study Amsterdam (FATIMA) trial, which monitored anti-factor Xa levels during therapy with t-PA and the LMWH nadroparin. From 12 h onward, 88% of all anti-factor Xa measurements fell within target range, obviating the need for coagulation monitoring. Arterial patency rates were high, and there were no major bleeding complications. Further support for LMWH in this setting has been provided by the ASSENT-PLUS trial. Preliminary data indicate that dalteparin, as an adjunct to t-PA and aspirin, is associated with a trend toward increased arterial patency rates compared with UFH, with a similar incidence of bleeding complications in both groups (Table III). However, there were no differences between the groups in the incidence of clinical events (death, reinfarction, revascularization) at 30 days.

The Second Trial of Heparin and Aspirin Reperfusion Therapy (HART II), in which 400 patients receiving accelerated t-PA were randomized to UFH or enoxaparin, confirmed that enoxaparin is at least as effective as UFH. Patency rates at 90 min were 80.1% in the enoxaparin group and 75.1% in the UFH group. Patients with patent arteries underwent a second angiogram at 5–7 days, and the

<table>
<thead>
<tr>
<th>Table III</th>
<th>Summary of clinical trials of low-molecular-weight heparin as an adjunct to fibrin-specific thrombolysis</th>
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<tbody>
<tr>
<td><strong>Trial</strong></td>
<td><strong>LMWH</strong></td>
</tr>
<tr>
<td>FATIMA³⁸</td>
<td>Nadroparin</td>
</tr>
<tr>
<td>ASSENT-PLUS³⁹</td>
<td>Dalteparin</td>
</tr>
<tr>
<td>HART II⁴⁰</td>
<td>Enoxaparin</td>
</tr>
<tr>
<td>ENTIRE-TIMI 23⁴¹</td>
<td>Enoxaparin</td>
</tr>
<tr>
<td>ASSENT-3³⁰</td>
<td>Enoxaparin</td>
</tr>
</tbody>
</table>

*Abbreviations: NS = not significant, FATIMA = Fraxiparin Anticoagulant Therapy in Myocardial Infarction Study Amsterdam, ASSENT = ASsessment of the Safety and Efficacy of a New Thrombolytic regimen, HART = Heparin and Aspirin Reperfusion Therapy, TIMI = Thrombolysis in Myocardial Infarction. Other abbreviations as in Tables I and II.*
rate of reocclusion was lower in the enoxaparin group than in the UFH group (5.9 vs. 9.8%). These benefits of enoxaparin were achieved without an increase in adverse events.

In the Enoxaparin and TNK-TPA with or without GP IIb/IIIa Inhibitor as REperfusion strategy in ST Elevation MI (ENTIRE-TIMI) 23 trial (n = 483), in which the thrombolytic regimen was full-dose tenecteplase, TIMI-3 flow rates at 60 min were similar in the UFH and enoxaparin groups (52 vs. 48–51%). It is important, however, that the rate of recurrent ischemic events at 30 days was 15.9% with UFH and 4.4% with enoxaparin (p = 0.005). The large, randomized, open-label ASSENT-3 trial (n = 6,095) showed that, as an adjunct to tenecteplase, enoxaparin reduced the primary endpoint (a composite of mortality, in-hospital reinfarction, or in-hospital refractory ischemia at 30 days) compared with UFH: 11.4 vs. 15.4%, relative risk 0.74, confidence interval (CI) 0.63 to 0.87 (p = 0.0002). This difference was driven by a reduction in in-hospital reinfarction and refractory ischemia in the enoxaparin group. Enoxaparin significantly reduced the incidence of the combined safety and efficacy endpoint compared with UFH: 13.7 vs. 17.0%, relative risk 0.81, CI 0.70 to 0.93 (p = 0.0037). The risk of major hemorrhagic complications was similar for UFH and enoxaparin (2.2 vs. 3.0% p = not significant).

Despite the clinically useful data generated by the ASSENT-3 trial, it was not designed to test a pre-specified hypothesis, and a larger confirmatory trial is planned, the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT-TIMI 25) trial. In this study the thrombolytic agent will not be specified and 20,000 patients will be randomized to either UFH or LMWH.

**Prehospital Fibrinolysis and LMWH**

There is unequivocal evidence that the earlier reperfusion is initiated, the greater the benefit. The mortality rate in enoxaparin-treated patients in the ASSENT-3 trial (5.4%) was among the lowest reported in a fibrinolytic trial, despite the median time-to-treatment (2.7 h) being similar to other studies. A protocol of bolus thrombolytic therapy followed by LMWH lends itself to prehospital thrombolysis, which may improve these results even further. This strategy has been investigated in the ASSENT-3 PLUS study by comparing patients treated with tenecteplase plus prehospital UFH or LMWH. In this study, which enrolled 1,639 patients, treatment with LMWH tended to lower the frequency of in-hospital ischemic complications or death at 30 days (14.2 vs. 17.4% for UFH, p=0.080), although there was no difference for this composite endpoint plus in-hospital intracranial hemorrhage or major bleeding. The increased intracranial hemorrhage was seen exclusively in patients >75 years of age and has been attributed to the lower creatinine clearance in elderly patients. In the ExTRACT-TIMI 25 study, the enoxaparin dose has been reduced in patients over the age of 75.

**Conclusions**

Fibrinolytic therapy remains the most widespread form of reperfusion therapy for STEMI. Adjunctive therapy with LMWH offers significant practical advantages compared with UFH. Randomized clinical trials have shown that LMWH is at least as effective as UFH as an adjunct to both fibrin-specific and streptokinase-based thrombolytic regimens. Low-molecular-weight heparin also has more favorable effects on secondary ischemic events following STEMI, and the clinical benefits are achieved without an increase in major bleeding or thrombocytopenia. These clinical advantages, together with its convenience and modest cost, ensure that LMWH should evolve as the adjunctive antithrombotic agent of choice for patients with STEMI.

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