The Role of Low-Molecular-Weight Heparin in the Management of Acute Coronary Syndromes

Marc Cohen, MD, FACC
Newark, New Jersey

A substantial number of clinical studies have consistently demonstrated that low-molecular-weight heparin (LMWH) compounds are effective and safe alternative anticoagulants to unfractionated heparins (UFHs). They have been found to improve clinical outcomes in acute coronary syndromes and to provide a more predictable therapeutic response, longer and more stable anticoagulation, and a lower incidence of UFH-induced thrombocytopenia. Of the several LMWH agents that have been studied in large clinical trials, including enoxaparin, dalteparin, and nadroparin, not all have shown better efficacy than UFH. Enoxaparin is the only LMWH compound to have demonstrated sustained clinical and economic benefits in comparison with UFH in the management of unstable angina/non-ST-segment elevation myocardial infarction (NSTEMI). Also, LMWH appears to be a reliable and effective antithrombotic treatment as adjunctive therapy in patients undergoing percutaneous coronary intervention. Clinical trials with enoxaparin indicate that LMWH is effective and safe in this indication, with or without the addition of a glycoprotein IIb/IIIa inhibitor. The efficacy demonstrated by enoxaparin in improving clinical outcomes in unstable angina/NSTEMI patients has led to investigations of its role in the management of ST-segment elevation myocardial infarction. Initial results are very encouraging, and they indicate that enoxaparin may potentially substitute for UFH as adjunctive therapy in fibrin-specific thrombolytic regimens and improve coronary reperfusion rates in streptokinase-based regimens.

Acute coronary syndrome (ACS) refers to a constellation of distinct clinical entities with a common etiology: an abrupt imbalance between myocardial oxygen supply and demand (i.e., myocardial ischemia) secondary to an acute plaque disruption or erosion (1,2). The ST-segment elevation on the presenting electrocardiogram indicates ST-segment elevation myocardial infarction (STEMI) in the presence of abnormal cardiac biomarkers, whereas patients who present without ST-segment elevation are experiencing either unstable angina (UA) or a non-STEMI (NSTEMI). The distinction between these two diagnoses is ultimately made based on the presence or absence of specific cardiac biomarkers such as troponin I or T, or creatine kinase–myocardial band (1,2).

Disruption or erosion of atherosclerotic plaque exposes oxidized low-density lipoprotein particles and tissue factor to flowing blood, which activates the coagulation cascade (2) (Fig. 1). This triggers platelet adhesion, aggregation and fibrin deposition, the subsequent entrapment of red blood cells, and ultimately the formation of a thrombus obstructing the coronary artery (1,2).

CURRENT MANAGEMENT OF ACS

The pharmacological treatment of ACS is designed to prevent the progression of UA/NSTEMI to MI or death. The optimal therapeutic approach currently recommended by the American College of Cardiology/American Heart Association guidelines includes a combination of antiplatelet and antithrombotic therapy (2). These guidelines recommend prompt initiation of aspirin (or a thienopyridine if aspirin is not tolerated) and the addition of an anticoagulant agent, such as unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). A platelet glycoprotein (GP) IIb/IIIa receptor antagonist should be added if ischemic pain continues (2), or in high-risk subjects. Clopidogrel is also recommended for patients not going to catheterization and bypass surgery (3).

LMWH VERSUS UFH

Although UFH was the standard anticoagulant, LMWH constitutes an effective alternative antithrombotic therapy to UFH, and it has a more favorable pharmacokinetic profile and several clinical advantages (4). Both UFH and LMWH act by binding to antithrombin III, an endogenous inhibitor of Factors Xa and thrombin IIa. This binding induces a conformational change in antithrombin 3, which markedly accelerates its ability to inactivate these factors. The LMWH compounds have a greater bioavailability than does UFH, are more resistant to inhibition by activated platelets, have a higher anti-Factor Xa:IIa activity ratio, and a more predictable anticoagulant effect (4,5). Therefore, LMWH can be administered subcutaneously in fixed doses, without the need to monitor activated partial thromboplastin time (aPTT) (5). In contrast, UFH usually requires intravenous administration and constant monitoring and adjustment of dosages (4). Moreover, LMWH is associated with a lower incidence of adverse side effects compared to UFH.
including heparin-induced thrombocytopenia and osteoporosis (5).

A newer member of the LMWH family, fondaparinux, is currently under clinical investigation. Fondaparinux is a synthetic heparin pentasaccharide with selective anti-Factor Xa activity (6). This compound displays a pharmacokinetic profile comparable to LMWH, but with no anti-Factor IIa activity.

Two LMWH compounds are Food and Drug Administration–approved for the treatment of UA/NSTEMI: enoxaparin (also approved for the treatment of venous thrombosis) and dalteparin. Other LMWH agents available include tinzaparin (approved for the treatment of venous thrombosis), nadroparin, and ardeparin (5). The LMWH compounds have distinct properties that may translate into differences in their clinical efficacy, and they are not interchangeable (7,8).

**Figure 1.** The coagulation cascade. Interaction of the intrinsic pathway (initiated by the activation of Factor XI) and the extrinsic pathway (activated by vascular or tissue injury) results in a cascade of reactions that generate thrombin (Factor IIa). Thrombin is produced from prothrombin Factor II by the action of activated Factor X (Xa). Thrombin then acts on fibrinogen to generate fibrin, which undergoes crosslinking, resulting in a thrombin–fibrin clot.

**Figure 2.** ESSENCE study: One-year follow-up trial results. Significant reductions were found in the composite end point of cardiovascular death, myocardial infarction (MI), and recurrent angina with enoxaparin treatment compared to treatment with unfractionated heparin (UFH). The need for diagnostic catheterization and coronary revascularization was also significantly reduced with enoxaparin treatment. ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events. Reprinted with permission from the American College of Cardiology Foundation, J Am Coll Cardiol 2000;36:693–8.

**ROLE OF LMWH IN THE TREATMENT OF ACS**

Two major double-blinded, randomized, placebo-controlled trials have been conducted to assess the use of enoxaparin in patients with UA/NSTEMI. The Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events (ESSENCE) trial randomized 3,171 patients to receive either subcutaneous enoxaparin 1 mg/kg twice daily, or UFH as a continuous IV infusion, both for two to eight days (9). After 14 days, patients who had been treated with enoxaparin had a significantly reduced risk of death, MI, or recurrent angina compared to those who received UFH (16.6% vs. 19.8%; p = 0.019). This significant benefit was sustained at 30 days (p = 0.016). The incidence of major bleeding complications was similar in both groups; an increase in minor bleeding was observed with enoxaparin, mainly attributable to ecchymoses at the injection site (9).

One-year follow-up results of the ESSENCE study indicate that the significant reduction with enoxaparin in the incidence of the composite end point was maintained (32.0% vs. 35.7%; p = 0.022) (10) (Fig. 2). Also, the need for diagnostic catheterization and coronary revascularization
Death, MI or recurrent angina

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Figure 3. Meta-analysis of low-molecular-weight heparin (LMWH) trials in unstable angina/non-ST-segment elevation myocardial infarction: ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events; FRAXIS = FRAXiparine in Ischemic Syndromes; FRIC = FRAgmin In unstable Coronary artery disease; LMWH = low-molecular-weight heparin; RRR = relative risk ratio; TIMI = Thrombolysis in Myocardial Infarction; UFH = unfractionated heparin. Adapted from Semin Thromb Hemost 1999;25 Suppl 3:113–21 (Fig. 3), with permission from Thieme Publishers, 2002.

was significantly reduced with enoxaparin compared to UFH (55.8% vs. 59.4%, p = 0.036, and 35.9% vs. 41.2%, p = 0.002, respectively) (10). A substudy of ESSENCE has also shown that treatment with enoxaparin is more likely to reduce rebound ischemia than UFH (11).

The Thrombolysis in Myocardial Infarction (TIMI)-11B trial randomly assigned 3,910 UA/NSTEMI patients to treatment with either enoxaparin or UFH for three to eight days in an acute treatment phase (11). In the outpatient phase, treatment with enoxaparin was continued for an additional 35 days, and the UFH-treated group was switched to placebo. At 14 days, there was a 15% reduction in the composite end point of death, MI, or recurrent angina with enoxaparin (14.2% vs. 16.7%; p = 0.029). This benefit was maintained at 43 days. However, long-term treatment did not confer any additional reduction in death and MI (12).

Interestingly, the TIMI-11B investigators have recently shown that prior aspirin use in patients with UA/NSTEMI is associated with a 60% higher risk of death and cardiac ischemic events compared with nonprior aspirin users (13). This subanalysis of ESSENCE and TIMI-11B demonstrated that prior aspirin users treated with enoxaparin had a reduced rate of death, MI, or urgent revascularization at days 8 and 43 compared with prior aspirin users taking UFH. In a prospectively planned meta-analysis of the TIMI-11B and ESSENCE studies, a significant reduction in the composite end point of death and MI with enoxaparin compared to UFH was demonstrated at 43 days (7.1% vs. 8.6%; p = 0.02) (14). When recurrent angina leading to urgent revascularization was included to form a triple, composite end point, event rates were 15.6% versus 18.8%, respectively (p = 0.0005). A subgroup analysis of TIMI-11B illustrated the variability associated with UFH in the aPTT levels achieved (15), and that treatment with enoxaparin provided better clinical outcomes for patients compared with every level of anticoagulation with UFH. The clinical superiority of enoxaparin in the management of patients with NSTEMI may be explained by its more predictable anticoagulant effect (a characteristic of LMWH). Indeed, it is difficult to maintain a target aPTT level with UFH.

Cost-effectiveness. Pharmacoeconomic analyses based on data from the ESSENCE study indicate that enoxaparin may also represent a cost-effective alternative to UFH (16–19). These analyses have shown that the beneficial effects of enoxaparin translate into significant cost savings (16–19). A recent study from the United Kingdom based on the ESSENCE one-year data showed that the early economic benefits of enoxaparin are also maintained in the longer term (19).

The FRISC trials. The efficacy of dalteparin in the management of ACS has been evaluated in the FRArm In During InStability in Coronary artery disease (FRISC) study. This trial randomized 1,506 patients admitted with an ischemic episode to either subcutaneous dalteparin 120 IU/kg twice daily, or placebo, for six days, followed by continued treatment with either placebo or a lower dose of dalteparin (7,500 IU subcutaneously, once daily) for 35 to 45 days (19). A significant benefit from treatment with dalteparin was observed at six days. However, after 150 days, there was no significant clinical benefit with dalteparin treatment.

In the FRISC II study, patients were randomized to either dalteparin or placebo for three months, as well as to invasive or noninvasive treatment. The combined end point of death and MI was lower in the dalteparin-treated patients in the noninvasive arm at one month, but not at three months or one year in either the noninvasive or the invasive group (20,21).

The FRIC study. The FRAgmin In unstable Coronary artery disease (FRIC) trial compared the efficacy of dalteparin versus UFH in 1,482 UA/NSTEMI patients (22). During the first six days of treatment, patients randomly received either subcutaneous dalteparin or continuous IV UFH infusion. Then, in a double-blind 45-day phase, subjects received dalteparin 7,500 IU once daily or placebo. The incidence of death, MI, or recurrent angina in the acute phase was similar in the UFH and dalteparin groups (7.6% vs. 9.3%; p = 0.33). Prolonged (45-day) treatment with dalteparin did not confer any additional benefit. A similar incidence of major bleeding complications was observed in both groups. These results suggest that treatment with dalteparin is equivalent to treatment with UFH in patients with UA/NSTEMI.

The FRAXIS study. The double-blind, randomized FRAXiparine in Ischemic Syndromes (FRAXIS) trial examined the efficacy of the LMWH nadroparin compared to UFH in 3,468 patients with UA/NSTEMI. The effects of acute-phase (6-day) treatment with UFH and nadroparin (86 IU/kg) were compared, and the effect of an extended (14-day) period of treatment with nadroparin (86 IU/kg) was also evaluated (23). No significant differences existed in clinical outcomes (cardiac death, MI, refractory angina, and
recurrence of UA), but the incidence of major hemorrhage was higher in the 14-day nadroparin group. The results of FRAXIS indicate that nadroparin has a similar efficacy to UFH in the treatment of ACS, but that a prolonged nadroparin regimen does not offer any additional clinical benefit.

A meta-analysis of results from the four LMWH trials, FRAXIS, FRIC, TIMI-11B, and ESSENCE, illustrates the superiority of enoxaparin to UFH in the reduction of primary end points (Fig. 3).

The PENTUA study. The PENT Ascachadine in Unstable Angina (PENTUA) study was a phase 2, randomized, dose-ranging trial comparing fondaparinux to enoxaparin in the treatment of 1,147 ACS patients with NSTEMI (24). Four daily doses of subcutaneous fondaparinux were tested (2.5, 4, 8, and 12 mg), as well as enoxaparin (administered subcutaneously at 1 mg/kg twice daily). The mean treatment duration was five days. The primary end point of death, MI, and recurrent ischemia at day 9 occurred in 37% of patients in the fondaparinux groups and in 40% in the enoxaparin group. Patients receiving the lowest dose of fondaparinux (2.5 mg) had the fewest primary end point events at day 9 (30%), significantly lower than the enoxaparin group and the groups receiving fondaparinux 4 and 8 mg (p < 0.05). The primary end point of death, MI, and recurrent ischemia at day 30 was also lower, with the lowest dose of fondaparinux (33.8%), compared to the enoxaparin group (43.6%), and to the groups treated with fondaparinux 4 and 8 mg (44.9%, 42.4%, 37.8%, respectively). Bleeding rates were similarly low in all treatment groups. No incidence of major bleeding occurred with the lowest dose of fondaparinux or with enoxaparin. The results of PENTUA indicate that fondaparinux is at least as effective as enoxaparin in reducing the occurrence of thrombotic events in ACS patients.

LMWH IN CORONARY INTERVENTION PROCEDURES

A number of randomized trials have demonstrated the significant benefits of GP IIb/IIIa inhibitors in patients undergoing percutaneous coronary intervention (PCI) (25). By inhibiting the activity of GP IIb/IIIa receptors on the platelet surface, GP IIb/IIIa inhibitors exert a direct anti-aggregatory effect by preventing circulating fibrinogen from interacting with platelet surfaces where it produces cross-linkage of platelets, aggregation, and ultimately thrombus formation (26–28). Because LMWH appears to offer several pharmacological and practical advantages over UFH, the safety and efficacy of LMWH, with or without GP IIb/IIIa blockers, has been investigated in patients with UA/NSTEMI who are candidates for PCI.

In a recent study (29), enoxaparin was administered subcutaneously at 1 mg (100 IU)/kg every 12 h for at least 48 h to 451 ACS patients, 65% (n = 213) of whom had a coronary angiography within 8 h of enoxaparin administration, followed by immediate PCI (n = 132; 28%). No increase occurred in the rate of major bleeding in patients undergoing PCI compared to those not undergoing cathe-
The efficacy and safety of the synthetic heparin pentasaccharide, fondaparinux, were assessed in the PENTALYSE study in patients (n = 333) with evolving STEMI (39). Subjects were randomized to treatment with either intravenous UFH during 48 to 72 h, or fondaparinux at dosages of 4 to 6 mg, 6 to 10 mg, or 10 to 12 mg daily for five to seven days. Patients underwent coronary angiography at 90 min and on days five to seven. Treatment with fondaparinux was associated with a trend toward less reocclusion of the infarct-related artery on days five to seven compared with UFH (0.9% vs 7.0%; p = 0.065) in patients who did not undergo coronary intervention (n = 155). During the 30-day follow-up period, fewer revascularization procedures were performed in the fondaparinux group (396% vs. 51% for UFH; p = 0.054). Of the 241 patients in the fondaparinux group, 1 (0.4%) had a nonfatal intracranial hemorrhage. The study (39) indicates that fondaparinux given with alteplase is safe and as effective as UFH in restoring coronary artery patency in patients with STEMI.

CLINICAL OUTCOME TRIALS

The FRAgmin in acute Myocardial Infarction (FRAMI) study and the BIOchemical Markers in Acute Coronary Syndromes (BIOMACS) II study have shown trends indicating that dalteparin may potentially improve clinical outcomes when used as an adjunctive treatment to streptokinase (40,41). However, in the FRAMI study, this benefit was at the expense of increased bleeding risk. In comparison, previous large trials evaluating the use of UFH and streptokinase as combination therapy have not reported improvements in clinical outcomes (42).

In the ASSENT PLUS study (43), dalteparin was compared to UFH as adjunctive treatment to thrombolysis with tPA. Dalteparin significantly reduced the occurrence of reinfarction in patients with acute MI, compared to UFH. Bleeding rates were similar.

The Acute Myocardial Infarction–Streptokinase (AMI-SK) study was recently conducted to evaluate the safety and efficacy of enoxaparin versus placebo in patients receiving streptokinase (44). The AMI-SK trial included 496 MI patients who were randomized to treatment with either enoxaparin (30 mg intravenous bolus followed by a subcutaneous dose of 1 mg/kg every 12 h) or placebo. The TIMI-3 flow at 5 to 10 days was significantly improved in the enoxaparin group (p = 0.01), as was the combined TIMI-2/3 flow (p = 0.001), leading to a significant reduc-
tion in clinical ischemic events, without a significant increase in bleeding.

The Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-3 trial (45) compared the fibrinolytic agent tenecteplase, combined with enoxaparin or abciximab, with tenecteplase plus UFH. Patients (n = 6,095) were randomized within 6 h of the onset of an acute MI to single-bolus tenecteplase plus subcutaneous enoxaparin, tenecteplase plus UFH (48-h infusion adjusted to maintain aPTT between 50 to 70 s), or half-dose tenecteplase plus IV UFH and IV abciximab. The combined end point of 30-day mortality, in-hospital reinfarction, or refractory ischemia was significantly lower in the enoxaparin and abciximab groups (11.4% and 11.1%, respectively; p = 0.0001) than in the UFH group (15.4%) (45). The efficacy and safety end point (30-day mortality, in-hospital reinfarction, or refractory ischemia, intracranial hemorrhage, or other major bleeding) also occurred less frequently (p = 0.0081) in the enoxaparin and abciximab groups (13.8% and 14.2%, respectively) compared to the UFH group (17.0%). Results of the ASSENT-3 trial suggest that the combination of full-dose tenecteplase and up to seven-day administration of enoxaparin would be the best treatment for patients with acute MI of < 6 h.

ONGOING STUDIES WITH LMWH

Several trials have been undertaken to optimize reperfusion therapy in STEMI and to evaluate the potential benefit of triple-combination therapy with a GP IIb/IIIa inhibitor. One such study, the ENOXaparin plus Tenecteplase-tPA wIthout GP IIb/IIIa as REperfusion for STEMI study (ENTIRE), is evaluating the use of enoxaparin with abciximab and tenecteplase.

Many patients do not receive any reperfusion therapy because they present too late, or have significant contraindications (46). The ongoing TETAMI study (47) is investigating the effect of enoxaparin versus UFH, with or without tirofiban, on the outcome of patients who are not candidates for thrombolytic therapy or PCI. The ongoing multinational Superior Yield of the New strategy of Enoxaparin, Revascularization & GIYcoprotein IIb/IIIa inhibitors (SYNERGY) trial has enrolled over 8,000 patients in over 400 centers. Its goal is to evaluate the efficacy and safety of enoxaparin versus UFH as first-line management in higher-risk NSTE ACS patients who are likely to also receive treatment with GP IIb/IIIa (eptifibatide) and undergo immediate catheterization and, if necessary, revascularization. The clinical end points of the trial are death, MI, major and minor hemorrhage, and all incidents of bleeding.

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Reprint requests and correspondence: Dr. Marc Cohen, Division of Cardiology, Newark Beth Israel Medical Center, 201 Lyons Avenue, Newark, New Jersey 07112. E-mail: marc.cohen@sbhcs.com.
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