

# The role of low-molecular-weight heparin in the management of acute coronary syndromes

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Optimized medical treatment for the non-ST segment elevation acute coronary syndromes (NSTE ACS) should consist of a combined antithrombotic/anti-anginal regimen. Standard antithrombotic treatment is currently unfractionated heparin and aspirin, and in high-risk patients glycoprotein IIb/IIIa inhibitors. However, low-molecular-weight heparins (LMWHs) have practical and clinical advantages over UFH and can be considered an effective alternative in the medical treatment of ACS and in patients proceeding to surgical interventions. Benefits include a more predictable and stable therapeutic response, no need for coagulation monitoring and a reduced incidence heparin-induced thrombocytopenia. In this context, the LMWH enoxaparin has demonstrated sustained clinical and economic benefits compared with UFH, with no increase in major bleeding complications. In addition, recently published studies indicate that LMWHs can improve reperfusion of the arteries and reduce reocclusion when used as adjunctive anticoagulant therapy in patients with ST segment elevation (STE) ACS undergoing thrombolysis with fibrin-specific agents or streptokinase. *Curr Opin Cardiol* 2001, 16:384–389 © 2001 Lippincott Williams & Wilkins, Inc.

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Current evidence suggests that all patients admitted with a diagnosis of non-ST segment elevation acute coronary syndromes (NSTE ACS) of unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) should be given optimized medical treatment on admission to stabilize their condition, with high-risk patients proceeding to early surgical intervention [1,2]. Optimized medical treatment of patients with NSTE ACS should include anti-anginal medication combined with an intensive antithrombotic regimen. The introduction of low-molecular-weight heparins (LMWHs, *eg*, enoxaparin, dalteparin) and platelet glycoprotein (GP) IIb/IIIa receptor antagonists offers the potential for more aggressive treatment regimens and has improved clinical outcomes in patients with acute coronary syndromes (ACS) [3–7]. This review summarizes the clinical evidence for the use of the various LMWHs in the management of ACS, both in a conservative medical strategy and as adjunctive therapy in coronary interventions. Lastly, recently released data on the management of STE ACS will be reviewed.

## Optimizing antithrombotic treatment in ACS

Disruption of coronary atherosclerotic plaques or endothelial erosion is a fundamental pathogenic event in the development of ACS. Disruption or erosion of vulnerable plaques triggers platelet activation, adherence and aggregation, and also the exposure of tissue factor, which activates the clotting cascade. Ultimately, this process leads to the production of an occlusive thrombus [8]. A combined antiplatelet and anticoagulation regimen is therefore a rational antithrombotic approach to the medical management of ACS, and recent guidelines recommend the use of oral aspirin and intravenous unfractionated heparin (UFH) or LMWH and for all patients with NSTE ACS unless contraindicated [1,2]. However, a number of problems are associated with UFH use, including the unpredictability of UFH binding to plasma proteins, rebound thrombosis, and the limited efficacy of UFH against platelet- and clot-bound thrombin [9].

Low-molecular-weight heparins represent an effective alternative antithrombotic therapy to UFH with a more favorable pharmacokinetic profile and a number of clinical advantages. Compared with UFH, LMWHs have a greater bioavailability, are resistant to inhibition by activated platelets, have a higher ratio of anti-Factor Xa:IIa activity, and offer more predictable therapeutic response

[9–11]. Practically, LMWHs can be administered subcutaneously in fixed doses, without the need to monitor activated partial thromboplastin time (aPTT) [11]. On a clinical level, LMWHs offer more effective and stable anticoagulation, potentially reducing the risk of rebound ischemic events [12•], and are associated with a lower incidence of osteoporosis and heparin-induced thrombocytopenia than UFH [13,14].

**Role of LMWHs in the management of ACS**

A number of LMWHs (enoxaparin, dalteparin, and nadroparin) have been clinically evaluated for use in patients with NSTEMI ACS. LMWHs do share class properties, but are chemically distinct and have individual clinical profiles. Enoxaparin has demonstrated sustained benefit over UFH in the treatment of UA and NSTEMI [3,4,15]. Dalteparin, tested versus placebo, has shown better short-term results [16]. In addition, both dalteparin and nadroparin have shown efficacy equivalent to that of UFH in the acute treatment of ACS [17–19]. A recently published study may offer a rationale for the clinical differences between the LMWHs. An early increase in von Willebrand factor (vWf) release is an indicator of poor outcome in UA, and Montalescot and co-workers recently showed that there was a serious increase in vWf over the first 48 hours in patients treated with either UFH or dalteparin, whereas there was no rise in vWf in the enoxaparin-treated group [20•]. Such differences may partially explain the variation in clinical efficacy seen in clinical trials, but further studies in this area are required to elucidate the full picture.

**Clinical experience with LMWHs**

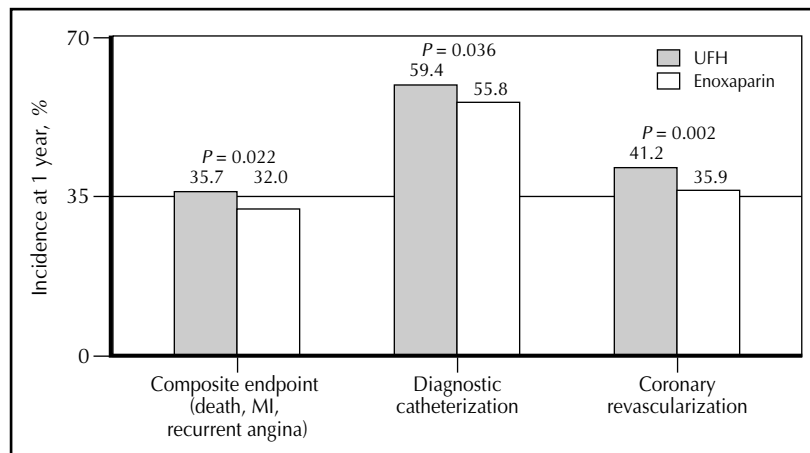
**Enoxaparin**

Two major double-blind, randomized, placebo-controlled trials have evaluated the use of enoxaparin in unstable coronary artery disease. The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial randomized 3171 pa-

tients with NSTEMI ACS to receive aspirin plus either enoxaparin, 1 mg/kg subcutaneously, or UFH as a continuous intravenous infusion, both for 2 to 8 days [3]. After 14 days, patients who had been treated with enoxaparin had a significantly lower risk of death, myocardial infarction (MI), or recurrent angina compared with those in the UFH group (16.6 vs 19.8%;  $P = 0.019$ ) and this benefit was still significant at 30 days ( $P = 0.016$ ). Importantly, the recently published 1-year follow-up results of the ESSENCE study [21•] highlight that the significant reduction in the incidence of the composite endpoint was maintained in the long-term in the enoxaparin group compared with those who received UFH (32.0 vs 35.7%;  $P = 0.022$ ) (Fig. 1). Moreover, at 1 year, the need for diagnostic catheterization and surgical revascularization was lower in the enoxaparin group than in the UFH group (55.8 vs 59.4%,  $P = 0.036$ , and 35.9% vs 41.2%,  $P = 0.002$ , respectively) [21•]. A substudy of ESSENCE has also shown that therapy with enoxaparin is more likely to prevent rebound ischemia than UFH. In the enoxaparin group, rebound ischemia occurred less frequently, the time to rebound ischemia was longer, and the duration of ischemic episodes was shorter [12•]. There was no difference between enoxaparin and UFH in the incidence of major bleeding complications in the ESSENCE study; the increase in minor bleeds observed with enoxaparin was mainly attributable to injection site ecchymoses [3].

Further evidence to support the clinical benefit of enoxaparin in patients with NSTEMI ACS was provided by the Thrombolysis In Myocardial Infarction (TIMI) 11B study [4]. A total of 3910 patients were randomly assigned either enoxaparin or UFH for 2 to 8 days in the acute treatment phase. In the outpatient phase, treatment with enoxaparin was continued and the UFH-treated group was switched to placebo. All patients received aspirin. At 14 days the results mirrored those of ESSENCE: there was a 15% reduction in the composite

**Figure 1. Sustained improvement**



Sustained improvement in clinical outcomes with enoxaparin – 1-year results of the ESSENCE study (from reference 15).

endpoint of death, MI or recurrent angina in the enoxaparin-treated group (16.7 *vs* 14.2%;  $P = 0.029$ ). This benefit was maintained at 43 days, though long-term treatment did not confer any additional advantage in outcome.

Interestingly, the TIMI 11B investigators have recently shown that prior aspirin use in patients with NSTEMI ACS is associated with a 60% increase in risk of death and cardiac ischemic events [22]. In this sub-analysis, 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 the prospectively planned meta-analysis of the TIMI11B and ESSENCE studies [15], a significant reduction in the “hard” composite endpoint of death and myocardial infarction was observed with enoxaparin versus UFH (7.1 *vs* 8.6%, odds ratio 0.82; 95% confidence interval 0.69 to 0.97;  $P = 0.02$ ). When recurrent angina leading to urgent revascularization is included to form a composite triple endpoint, event rates are 15.6 versus 18.8% (Odds ratio 0.80; 95% confidence interval 0.71-0.91;  $P = 0.0005$ ).

One of the possible reasons for the clinical superiority of enoxaparin in the management of NSTEMI ACS is the more stable anticoagulant effect they provide, given the difficulty in maintaining a target aPTT level with UFH. A subgroup analysis of TIMI 11B [23•] highlighted that UFH is associated with variability in the aPTT levels achieved with UFH. This analysis has also shown that treatment with enoxaparin results in better clinical outcomes for patients compared with every level of anticoagulation with UFH, with no significant increase in major bleeding rates [23•].

In the treatment of NSTEMI ACS, guidelines indicate that GPIIb/IIIa inhibitors should be given in high-risk patients. As a result, studies are under way to confirm the safety of enoxaparin with these compounds in NSTEMI ACS. A small study in 55 patients with NSTEMI ACS showed that the combination of tirofiban and enoxaparin was safe and did not adversely affect the pharmacodynamics of tirofiban, when compared with UFH [24]. A subsequent larger safety study (ACUTE II) has been completed and will be published soon. In addition, the ongoing A-Z trial is evaluating tirofiban with either enoxaparin or UFH in over 5000 UA/NSTEMI patients.

In addition to the improvements in clinical outcomes seen with enoxaparin as an alternative antithrombotic treatment for patients with NSTEMI ACS, cost-effectiveness data have been generated by pharmacoeconomic assessments based on data from the ESSENCE study. These data have shown that the improvement in clinical outcomes and the reduction in revascularization

procedures that result from treatment with enoxaparin translate into an absolute cost saving [25–28•]. Most recently, the ESSENCE 1-year data have been used to show that the early economic benefits of enoxaparin are also maintained in the longer term [28•].

### Dalteparin

The efficacy of dalteparin in the management of ACS has been investigated in several large clinical trials. The Fragmin during instability in coronary artery disease (FRISC) study randomized 1506 patients admitted with an ischemic episode to either aspirin, dalteparin (120 IU/kg s.c. twice daily) or placebo for 6 days, followed by continued treatment with either aspirin and placebo or a lower dose of dalteparin (7500 IU subcutaneously once daily) for 35 to 45 days [16]. At 6 days, a significant benefit from treatment with dalteparin was observed, but the improvement in clinical outcomes decreased over time and by 150 days the clinical advantage with dalteparin treatment was not significant.

The FRISC II study investigated the effects of short- and long-term treatment with dalteparin. After 5 days of open-label treatment with aspirin, dalteparin, patients were randomized to 3 months of treatment with either dalteparin or placebo and all patients continued on aspirin. The combined endpoint of death and MI was lower in the dalteparin-treated patients in the noninvasive arm at 1 month, but at 1 year no significant benefit of the 3-month treatment with dalteparin was seen in either the noninvasive or the invasive group [16,29•].

The FRagmin In unstable Coronary artery disease (FRIC) trial directly compared the efficacy of UFH and dalteparin in approximately 1500 patients [18]. All patients also received aspirin. The incidence of death, MI or recurrent angina in the acute phase (up to 6 days) was similar in the groups receiving treatment with UFH and dalteparin (7.6 *vs* 9.3%; not significant), and prolonged dalteparin treatment (45 days) did not confer any additional benefit over aspirin alone. The incidence of major bleeding complications was similar in both groups.

### Nadroparin

The double-blind, randomized Fraxiparine in ischemic syndromes (FRAXIS) trial compared the effects of acute-phase (6-day) treatment with UFH and nadroparin (86 IU/kg), and evaluated the effect of an extended (14-day) period of treatment with nadroparin (86 IU/kg) in patients with UA/NSTEMI [19]. There were no significant differences in the clinical outcomes of the three groups, though the incidence of major hemorrhage was higher in the 14-day nadroparin group. FRAXIS data indicate that nadroparin has an efficacy similar to that of UFH in the treatment of ACS, but that a prolonged nadroparin regimen does not offer any additional clinical benefit.

### Long-term LMWH treatment in NSTEMI ACS

In the TIMI 11B, FRIC and FRISC2 studies, extended treatment beyond the 8-day acute treatment period with LMWH was tested versus placebo treatment. In all cases no benefit of extended LMWH treatment past the acute treatment period of 2 to 8 days was proven [4,17,18].

### LMWHs as adjunctive therapy in coronary intervention procedures

Recent trials have established a beneficial role for early catheterization and intervention [30,31]. The benefits of LMWHs have been demonstrated as part of a combined antithrombotic/antianginal treatment regimen in medical management of ACS. Currently, the efficacy of LMWHs as adjunctive therapy before and during interventional strategies is being investigated. Recently published clinical data indicate that treatment with enoxaparin (1 mg/kg twice daily) provides effective anticoagulation in patients with NSTEMI ACS proceeding to percutaneous coronary interventions (PCI), without any significant increase in major bleeding complications [32•]. Further support for the efficacy of enoxaparin therapy in over 1600 patients, with or without concomitant therapy with the GP IIb/IIIa inhibitor abciximab, has been shown by the National Investigators Collaborating on Enoxaparin (NICE) 1 and 4 study groups, respectively [33•]. Results from the NICE studies indicate that treatment with enoxaparin provided effective anticoagulation, comparable to that seen with weight-adjusted doses of UFH in previous PCI trials [the Evaluation of PTCA to improve long-term outcome by cF7E3 glycoprotein receptor blockade (EPILOG) trial and the Evaluation of platelet inhibition in stenting (EPISTENT) trial [33–36]]. The incidences of major and minor (non-intervention-related) bleeding events associated with enoxaparin were low and were not increased by the addition of abciximab. A further study, NICE3, which included patients treated with enoxaparin in combination with tirofiban, abciximab or eptifibatid has also been completed, and full results will be published soon.

Dalteparin is also being investigated as concomitant adjunctive treatment with abciximab during PCI. While studies with sufficient power to evaluate clinical efficacy are still required, a pilot dose-finding study has indicated that dalteparin, given as an intravenous dose of 60 IU/kg with abciximab, appears to provide safe and effective antithrombotic therapy in a small cohort of patients (N = 28) [36].

The potential of locally administered LMWH to reduce restenosis after coronary stent implantation has very recently been identified. In the Polish-American local Lovenox NIR Assessment (POLONIA) study, locally delivered enoxaparin significantly reduced late luminal loss compared to systemic heparinization ( $0.76 \pm 0.42$  mm vs

$1.07 \pm 0.49$  mm;  $P = 0.001$ ). Restenosis was also significantly reduced in the enoxaparin compared with the systemic-heparin group (10 vs 24%;  $P = 0.05$ ) [37•].

### Impact of LMWHs in patients with STEMI ACS

Antithrombotic therapy is a logical adjunct to thrombolytic therapy in the early treatment of patients with STEMI ACS. The rate and magnitude of coronary artery recanalization are increased and the risk of reocclusion is reduced, resulting in improved clinical outcomes. The proven clinical efficacy of enoxaparin in the management of NSTEMI ACS has led to investigation of a role for enoxaparin in STEMI ACS. Indeed, a recent subgroup meta-analysis of ESSENCE/TIMI 11B data has shown that enoxaparin treatment is superior to UFH in reducing the incidence of the triple endpoint of death, MI or emergency revascularization in the cohort of 252 patients included in these trials that developed Q-wave MI [38].

The Heparins and Aspirin Reperfusion Therapy (HART) II study recently showed that enoxaparin, used immediately in conjunction with tissue plasminogen activator (tPA), was slightly more effective (but statistical significance was not reached) than UFH in achieving infarct-related artery patency (TIMI 2 and 3 flow) 90 minutes after the start of treatment. Analysis of the per-protocol sample revealed that patients in the enoxaparin group exhibited a significantly lower reocclusion rate at days 5 to 7 without an increase in major bleeding [39]. A similar study (ASSENT PLUS), which directly compares dalteparin and UFH as adjunctive treatment to thrombolysis with tPA [40], has been completed and peer-reviewed publication is pending.

The Acute Myocardial Infarction-Streptokinase (AMI-SK) study investigated the safety and efficacy of enoxaparin versus placebo in patients receiving streptokinase [41]. Adjunctive therapy with enoxaparin was shown to facilitate early coronary reperfusion and improve angiographic patency 5–10 days after treatment, leading to a significant reduction in clinical ischemic events. The AMI-SK study is the first to report a significant clinical improvement with UFH-based anticoagulant therapy in patients receiving streptokinase. The Fragmin in acute myocardial infarction (FRAMI) study, and Biochemical markers in acute coronary syndromes (BIOMACS) II studies have shown trends indicating that dalteparin has the potential to improve clinical outcomes when used as treatment adjunctive to streptokinase [42,43], though in the FRAMI study this benefit was at the expense of increased bleeding risk. Previous meta-analyses evaluating the use of UFH and streptokinase as combination therapy have not reported improvements in clinical outcomes [44].

Several trials are ongoing to optimize reperfusion therapy in STEMI ACS and to evaluate the potential benefit of

triple combination therapy with a GP IIb/IIIa inhibitor. The ASSENT 3 study is investigating the use of tenecteplase with enoxaparin, UFH, or abciximab and UFH in 6095 patients. The results, which are expected soon, should help to optimize reperfusion therapy in AMI patients. A further study that has just completed, Enoxaparin plus TNK-tPA with/without GPIIb/IIIa as reperfusion for STEMI study (ENTIRE), also evaluates the use of enoxaparin with abciximab and tenecteplase. The Fibrinolytic and Aggrastat ST-Elevation Resolution Trial (FASTER) study, currently ongoing, will investigate the use of reduced doses of TNK-tPA in combination with tirofiban in STE ACS.

Presently, many patients do not receive any reperfusion therapy [45] because they present too late, or have significant contraindications to reperfusion therapies. The ongoing TETAMI study is investigating the effect of enoxaparin versus UFH, both with or without tirofiban on the outcome of these nonreperused patients [46].

## Summary

Low-molecular-weight heparins are effective alternative antithrombotic agents to UFH for the medical management of NSTEMI ACS, and their use offers the potential to improve clinical outcomes in these highly prevalent syndromes. Benefits of LMWHs include a more predictable therapeutic response, longer and more stable anticoagulation, and a lower incidence of osteoporosis and UFH-induced thrombocytopenia. Not all LMWHs have shown better efficacy than UFH; enoxaparin is the only agent to have demonstrated sustained clinical and economic benefits in comparison with UFH in the management of NSTEMI ACS. LMWHs also have potential to increase the intensity of antithrombotic treatment as adjunctive therapy in patients undergoing PCI. Clinical trials with enoxaparin indicate that LMWHs are effective and safe in this indication, with or without the addition of a GP IIb/IIIa inhibitor. Finally, the efficacy demonstrated by enoxaparin in improving clinical outcomes in NSTEMI ACS has led to investigations of the role of enoxaparin in the management of STE ACS. Initial results are promising, and indicate that enoxaparin has the potential to replace UFH as adjunctive therapy in fibrin-specific thrombolytic regimens and to improve coronary reperfusion rates in streptokinase-based regimens.

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