# Role of LMWH in ACS, with or without PCI and GP IIb/IIIa blockade

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## Abstract

**Low molecular weight heparin (LMWH) and unfractionated heparin (UFH) are used to prevent rethrombosis and distal platelet embolisation in acute coronary syndromes. LMWH have a more predictable anticoagulant response and are less likely to result in bleeding. For the moment UFH should be used in primary percutaneous coronary intervention (PCI). It may also be preferable to use UFH in the setting of rescue PCI following tenecteplase (TNK) treatment. In those over 75 years of age, the combination of TNK with enoxaparin has been shown to be superior to TNK with UFH in reducing ischaemic end points without increasing the risk of haemorrhage. Results from TIMI IIB indicate that enoxaparin is superior to UFH for the acute management of non-ST elevation ACS (in patients managed conservatively). Enoxaparin and UFH appear to have similar efficacy and safety profiles when used in conjunction with glycoprotein IIb/IIIa blockade during PCI.**


**Key words:** low molecular weight heparin, unfractionated heparin, acute coronary syndromes, percutaneous coronary intervention, glycoprotein IIb/IIIa blockade

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## Introduction

> *'Heparin and low molecular weight dextran are administered during dilatation; warfarin is started after the procedure and is continued until follow-up.'*[1]

Platelet thrombus formation, in the setting of an ongoing prothrombotic state, is central to the pathomechanism of acute coronary syndromes (ACS). Administration of an antithrombotic agent is essential to prevent rethrombosis and distal platelet embolisation in ACS, and to optimise the efficacy of short-acting thrombolytics in patients with ST elevation myocardial infarction (STEMI). In these settings, the superiority of heparin over placebo is undisputed. Low molecular weight heparins (LMWH) possess several advantages over unfractionated heparin (UFH), and several large-scale clinical trials have examined the safety and efficacy of these agents in the setting of ACS.

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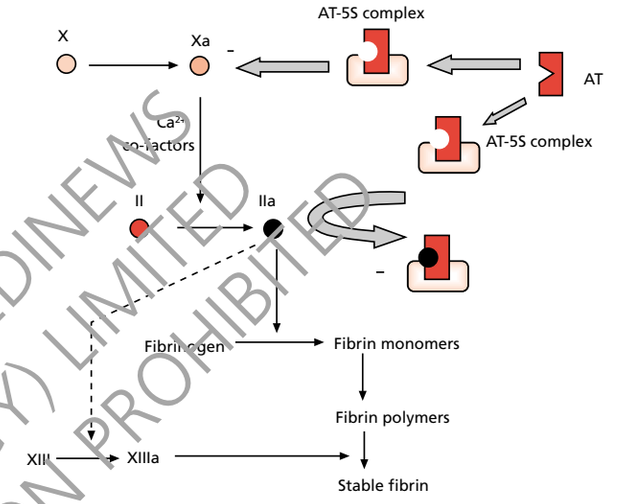
**Figure 1.** Antithrombotic and anticoagulant effects of heparin. Both UFH and LMWH contain a pentasaccharide sequence (5S) which, when bound to antithrombin (AT), results in a conformational change in AT which accelerates its interaction with activated factor X (Xa) and thrombin (IIa)




## Benefits of LMWH over UFH

Both LMWH and UFH contain a pentasaccharide sequence that allows binding to antithrombin, causing a conformational change that accelerates the interaction of antithrombin with thrombin (factor IIa) and with activated factor X (factor Xa) by a factor of 1,000 (figure 1). Both potentiate the action of antithrombin, but the main difference between UFH and LMWH is that UFH has similar inhibitory activity against both thrombin and factor Xa, whereas LMWH have four times greater activity against factor Xa. Additionally, both drugs exert an indirect anti-Xa effect by promoting the release of tissue-factor-pathway inhibitor from the endothelium, which inactivates factor Xa.

LMWH have a much more predictable anticoagulant

response than UFH since they do not bind to plasma proteins and renal elimination is dose-independent. In contrast, the extensive non-specific binding of UFH to serum proteins, macrophages and endothelial cells results in relatively low bioavailability, producing incomplete and variable inhibition of thrombin. The dose-dependent, biphasic (renal and hepatic) mode of elimination of UFH further compounds the variability in anticoagulant response.

LMWH are less likely to result in bleeding, not only because of their more predictable anticoagulant action, but also because they interfere less with platelet-vessel wall interactions due to their reduced affinity for platelets, von Willebrand factor (vWF) and endothelial cells.[2,3] The reduced affinity for platelets also underlies the reduced incidence of heparin-induced thrombocytopenia with LMWH compared with UFH.[4] Theoretically, the relative lack of platelet activation and the greater ability of LMWH to blunt the increase in vWF (a factor associated with worse outcomes in ACS) should provide antithrombotic properties additional to the superior anticoagulant effects.

The pharmacological advantages of LMWH obviate the need for plasma monitoring, except perhaps in patients with severe renal impairment, in patients who weigh < 50 kg or > 100 kg, and in pregnancy, where plasma anti-factor Xa activity should be monitored. Treatment with protamine neutralises the antithrombin effect but only partially reverses the anti-factor Xa activity of LMWH: it has nevertheless been successfully used to arrest bleeding caused by LMWH in animals.[5] This is likely to be due to the fact that the bleeding effect of UFH or LMWH is considered attributable to their anti-thrombin activity and for this reason, protamine may be used to neutralise LMWH if bleeding occurs.[6]

## LMWH in STEMI

### Primary percutaneous coronary intervention (PCI)

The role of LMWH in primary angioplasty or stenting for acute myocardial infarction (AMI) has not been evaluated. The ACC/AHA guidelines for procedural anticoagulation with UFH recommend achieving an activated clotting time (ACT) of 250–300s with the HaemoTec device and 350s with the Haemochron device.[7] There are no guidelines for procedural anticoagulation with LMWH.

The CADILLAC trial showed a favourable effect of abciximab during primary angioplasty but not during primary stenting.[8] However, when glycoprotein (GP) IIb/IIIa receptor antagonists are concomitantly used, the dose of UFH needs to be adjusted. Theoretically, therefore, the optimal level of anticoagulation with LMWH may also vary, depending on whether adjuvant abciximab is used. In patients receiving GP IIb/IIIa blockade, the guidelines recommend the dose of UFH be reduced to achieve a target ACT of 200 s, using either the HaemoTec or the Haemochron device.[7] There are no guidelines for using GPIIb/IIIa inhibitors with LMWH in the peri-procedural setting.

Since anticoagulation needs to be initiated early, at a stage when the need for stenting or abciximab may not be entirely clear, and since the anticoagulant effect of LMWH is not as readily reversible as that of UFH, for the present UFH (with or without abciximab) should be used until the results of prospective trials comparing LMWH with UFH in this setting become available.

### Rescue PCI

At present there is no evidence to support a policy of rescue angioplasty for failed thrombolysis, but this continues to be performed while definitive guidance from the ongoing REACT trial is awaited.[9] The role of LMWH in this setting has not been evaluated. Many, if not most, operators give abciximab peri-procedure during PCI for STEMI.

The decision to use LMWH in the setting of rescue PCI, where the patient has already received full-dose thrombolysis and is likely to receive a glycoprotein IIb/IIIa inhibitor, must be carefully considered. The only available data for combined thrombolytic therapy, abciximab and heparin come from thrombolytic trials for AMI. In ASSENT 3[10] the combination of half-dose tenecteplase, abciximab and UFH, and in GUSTO V[11] the combination of half-dose reteplase and abciximab and UFH increased flow in the infarct-related vessel, but did so at the cost of higher rates of thrombocytopenia, major bleeding complications and blood transfusions. Since the initial half-life of tenecteplase is 20–24 minutes, with a terminal half-life of 90–130 minutes, circulating levels may still be high at the time of rescue.

Therefore, in the setting of rescue PCI following tenecteplase treatment, it may be preferable to use UFH rather than LMWH, since the anticoagulant effect is more readily reversible should major bleeding complications arise.

### Thrombolysis

The first study to examine the efficacy of enoxaparin following thrombolytic therapy, HART II (Heparin and Aspirin Reperfusion Therapy), randomised patients following recombinant tissue plasminogen activator (rt-PA) administration to enoxaparin or UFH for three days. It showed that enoxaparin was at least as effective as UFH, with a trend towards a higher 90-minute patency rate and a reduced 7-day reocclusion rate (5.9% *vs.* 9.8%), most marked in those with TIMI 3 flow in the infarct-related artery post-thrombolysis.[12] Table 1 summarises some of the key trials using LMWH in ACS.

Subsequently, the efficacy of enoxaparin following various fibrinolytic therapies was assessed in a randomised trial of patients receiving streptokinase, anistreplase or rt-PA, followed by enoxaparin or UFH for four days. Enoxaparin reduced the composite 90-day end point of death, reinfarction or readmission with unstable angina from 36% to 26% without any increase in major haemorrhage.[13]

At the time of writing, rt-PA and streptokinase remain the most widely prescribed thrombolytics in the UK. April 2003 was the government's target for ensuring that 75% of eligible patients receive thrombolysis within 20 minutes of hospital arrival.[14] Given the inherent delays in setting up and administering infusions of streptokinase or rt-PA, this goal can, realistically, only be achieved with the use of pre-hospital thrombolysis and/or converting to thrombolysis with an agent that can be administered as a bolus injection, such as tenecteplase (TNK).

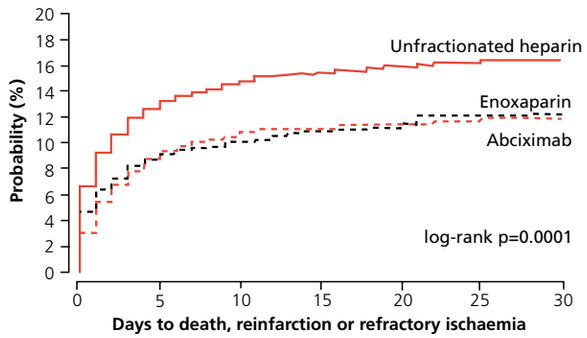
**Table 1.** Key clinical trials using LMWH in acute coronary syndromes

| Clinical syndrome | Trial name | No. pts | Management strategy (randomised to) | Other agents used | End point | Results |
|---|---|---|---|---|---|---|
| STEMI | HART II | 400 | UFH or enoxaparin for at least 3 d post-thrombolysis | All pts received rtPA | 90 min IRA patency rates & re-occlusion at 5–7 d | TIMI 2 or 3 flow in 80% *vs.* 75% enoxaparin *vs.* UFH and re-occlusion 5.9% *vs.* 9.8% enoxaparin *vs.* UFH |
| | Baird *et al.** | 300 | UFH or enoxaparin for 4 d post-thrombolysis | SK or rtPA or anistreplase | 90 d death/MI/ readmission with ACS | 36% *vs.* 26% enoxaparin *vs.* UFH |
| | ASSENT 3 | 6,095 | (1) Full-dose TNK + enoxaparin, (2) Half-dose TNK + UFH and abciximab, or (3) Full-dose TNK + UFH | TNK +/- abciximab | 30 d death/MI/ refractory ischaemia, and above + intracranial/ systemic haemorrhage | 11% *vs.* 11% *vs.* 15% for enoxaparin *vs.* abciximab *vs.* UFH (RR 0.74 with enoxaparin) |
| | ENTIRE-TIMI 23 | 483 | (1) Full-dose TNK + UFH, (2) Full-dose TNK + enoxaparin, (3) Half-dose TNK + abciximab + enoxaparin or (4) Half-dose TNK + abciximab + UFH | TNK +/- abciximab | 60 min TIMI 3 flow and 30 d death/recurrent MI | Similar TIMI 3 flow with enoxaparin and UFH 30 d event rate: full-dose TNK 16% *vs.* 4% for UFH *vs.* enoxaparin half-dose TNK 6.5% *vs.* 5.5% for UFH *vs.* enoxaparin |
| NSTEMI | FRISC | 1,506 | Dalteparin or placebo | None | Death/MI at 6 d | 1.8% *vs.* 4.8% for dalteparin *vs.* UFH |
| | FRIC | 1,482 | UFH or dalteparin for 6 d, then dalteparin or placebo for d 6–45 | None | 6 d and 45 d death/MI/ recurrent angina | 7.6% *vs.* 9.3% for dalteparin *vs.* UFH at 6 d 12.3% in both dalteparin and placebo arms at 45 d |
| | ESSENCE | 3,171 | Enoxaparin or UFH for 2-8 d | None | 14 d and 30 d death/ MI/recurrent angina and 30 d revascularisation | 17% *vs.* 20% at 14 d and 20% *vs.* 23% at 30 d in enoxaparin *vs.* UFH. 27% *vs.* 32% revascularisation enoxaparin *vs.* UFH |
| | TIMI-11B | 3,910 | UFH for ≥ 3 d f/by placebo or enoxaparin for up to 35 d post-discharge | None | 8 d and 43 d death/MI/ urgent revascularisation | 15% *vs.* 12% at 8 d for UFH *vs.* enoxaparin 20% *vs.* 17% at 43 d for UFH *vs.* enoxaparin |
| | GUSTO IV-ACS | 7,800 | 5 d dalteparin or 48 h UFH | Abciximab or placebo | 7 d bleeding 30 d death/MI | With abciximab, similar rates of stroke and major bleeding with dalteparin and UFH, but minor bleeds & thrombocytopenia more frequent with dalteparin Death/MI: 10% *vs.* 9% dalteparin *vs.* UFH (with abciximab); 11% *vs.* 8% dalteparin *vs.* UFH (with placebo) |
| ACS with PCI | FRISC 2 | 2,267 | 5 d in-hosp open label dalteparin f/by dalteparin or placebo for 3 m | None | 30 d and 3 m death/MI | At 30 d 3% *vs.* 6% dalteparin *vs.* placebo and at 3 months 7% *vs.* 8% dalteparin *vs.* placebo |
| | FRISC 2 | 2,457 | Early invasive *vs.* non-invasive treatment | Dalteparin or placebo for 3 m | 6 m death/MI | 9% *vs.* 12% invasive *vs.* non-invasive, irrespective of dalteparin |
| | TACTICS-TIMI 18 | 2,220 | Early invasive *vs.* non-invasive strategy | UFH and tirofiban for 48 h | 6 m death/MI/ rehospitalisation | 16% *vs.* 19% for invasive *vs.* non-invasive strategy |
| | RITA 3 | 1,810 | Early invasive *vs.* non-invasive strategy | Enoxaparin | Death/MI/refractory angina at 4 m and death/MI at 1 yr | 10% *vs.* 15% at 4 m invasive *vs.* conservative arm 8% in both groups at 1 year |
| | A to Z § | 3,985 | Enoxaparin or UFH | Tirofiban | Death/MI/refractory ischaemia at 7 d | 8% *vs.* 9% for enoxaparin *vs.* UFH |
| | SYNERGY | 8,000 | Enoxaparin *vs.* UFH at least until after PCI (open label) | Early PCI & GP IIb/IIIa encouraged | Death/MI at 30 d | Trial ongoing |

**Key:** m = months; d = days; IRA = infarct-related artery; TIMI = thrombolysis in myocardial infarction; ACS = acute coronary syndromes; PCI = percutaneous coronary intervention; TNK = tenecteplase; UFH = unfractionated heparin; SK = streptokinase; rtPA = recombinant tissue plasminogen activator; MI = myocardial infarction; GP = glycoprotein; f/by = followed by

*Baird SH, *et al. Eur Heart J* 2002;**23**:627-32; §A to Z trial, presented in abstract form at Late Breaking Clinical Trials, ACC, 2003.

**Figure 2.** Results of the ASSENT 3 trial. Kaplan-Meier curves for primary efficacy end point

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Two non-blinded studies have compared enoxaparin and UFH following thrombolysis with TNK for AMI. ASSENT 3 randomised some 6,000 patients with AMI to one of three regimens: full-dose TNK and enoxaparin for a maximum of seven days (enoxaparin group), half-dose TNK with weight-adjusted low-dose UFH and a 12-hour infusion of abciximab (abciximab group), or full-dose TNK with weight-adjusted UFH for 48 hours (UFH group).[10] Enoxaparin was given as an initial intravenous (iv) bolus, followed immediately by the first subcutaneous injection.

At 30 days, there were significantly fewer ischaemic end points in the enoxaparin and abciximab groups than in the UFH group: 11.4% *vs.* 15.4% (RR=0.74) for enoxaparin, and 11.1% *vs.* 15.4% (RR=0.72) for abciximab (figure 2). The same was true for the composite of ischaemic end points and major haemorrhage: 13.7% *vs.* 17.0% (RR=0.81) for enoxaparin, and 14.2% *vs.* 17.0% (RR=0.84) for abciximab.

The ENTIRE-TIMI 23 (Enoxaparin and Tenecteplase with or without glycoprotein IIb/IIIa Inhibitor as Reperfusion strategy in ST Elevation MI – Thrombolysis in Myocardial Infarction) study[15] randomised 500 patients with STEMI to one of three regimens: full-dose TNK with UFH or full-dose TNK with enoxaparin and half-dose TNK plus abciximab with either UFH or reduced dose enoxaparin. Although 60-minute TIMI 3 flow rates were similar with enoxaparin and UFH, enoxaparin exhibited significant advantages over UFH with respect to ischaemic events. Through 30 days, the risk of death or recurrent MI in the full-dose TNK with UFH group was 15.9% and only 4.4% with full-dose TNK with enoxaparin. In the combination therapy group, the rates were 6.5% with UFH and 5.5% with enoxaparin. These benefits of enoxaparin were achieved without incurring any additional risk of major haemorrhage over that seen with UFH.

The results of ASSENT 3 and ENTIRE-TIMI 23 show that enoxaparin in combination with TNK is at least equivalent at an early time-point (ENTIRE-TIMI 23), and possibly superior (ASSENT 3, ENTIRE-TIMI 23) to UFH through ischaemic end points at 30 days. In light of the efficacy and ease of administration, the combination of TNK plus enoxaparin is an extremely attractive reperfusion regimen.

Given the necessity for prompt reperfusion, pre-hospital thrombolysis is an attractive option. A satellite study, ASSENT-3 PLUS[16] was conducted to investigate the combination of TNK/enoxaparin versus TNK/UFH in the pre-hospital setting. Pre-hospital thrombolysis reduced the time to treatment by 45 minutes. Although the 30-day ischaemic end point of death, in-hospital AMI or refractory ischaemia was similar in the TNK/enoxaparin and the TNK/UFH groups (14.2% *vs.* 17.4%, respectively), there was an increase in intracranial haemorrhage in the TNK/enoxaparin group in patients aged more than 75 years. In those under 75, the combination of TNK/enoxaparin was superior to TNK/UFH in reducing ischaemic end points without increasing the risk of haemorrhage, suggesting that in this age group, pre-hospital thrombolysis with TNK/enoxaparin is safe and effective. Ongoing studies are evaluating the safety of reduced-dose TNK/enoxaparin combinations in those over 75 years.

## LMWH in UA/NSTEMI

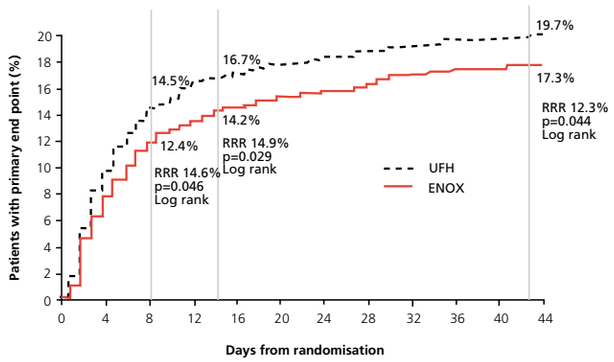
The FRISC study[17] evaluated the combination of aspirin and weight-adjusted dalteparin, given for up to 50 days, compared with aspirin alone. At six days, the incidence of death or AMI was only 1.8% in the LMWH group compared with 4.7% in the placebo group, representing a relative risk reduction of 48% with dalteparin. The FRIC study[18] subsequently compared the combination of aspirin with either dalteparin or UFH in 1,500 patients with ACS, but showed no difference in efficacy or safety between the two groups.

The ESSENCE trial[19] randomised patients with unstable angina (UA) to either enoxaparin or intravenous UFH, for a minimum of 48 hours and a maximum of eight days. The median duration of treatment was 2.6 days. Heparin was discontinued at the time of hospital discharge, a new MI or a revascularisation procedure. The primary end point of the composite of death/MI/recurrent angina at 14 days was reduced from 19.8% with UFH to 16.6% with enoxaparin. This benefit was maintained at 30 days (23.3% *vs.* 19.8%, respectively), without a significant difference in the incidence of major haemorrhage. The reduction in this composite end point was driven chiefly by a reduction in recurrent angina, although there were reductions in both deaths and MI at 30 days.

The differing results of FRIC and ESSENCE may be attributable to the differing anticoagulant properties of the two LMWH used. Dalteparin, used in FRIC, has an anti-factor Xa activity:anti-factor IIa activity ratio of 2:1, compared with 3:1 for enoxaparin (used in ESSENCE) in this respect, UFH more closely resembles dalteparin than enoxaparin.

Subsequently, the larger Thrombolysis In Myocardial Infarction (TIMI) 11B trial[20] randomised 4,000 patients with UA to receive UFH or enoxaparin over an acute phase of three days and a longer out-patient phase of 35 days. The primary end point was the com-

**Figure 3.** Results of the TIMI 11B trial. Kaplan-Meier plots of time to first event of primary end point to 43 days. Vertical dashed lines indicate comparisons at day 8 (end of acute phase), day 14 and day 43 (end of chronic phase)




**Key:** RRR = relative risk reduction; ENOX = enoxaparin; UFH = unfractionated heparin

Figure reprinted from *Circulation* 1999;**100**:1593-601[20] with permission from Lippincott Williams and Wilkins

posite of death, MI or urgent revascularisation. By 48 hours of treatment, the Kaplan-Meier curves for the composite end point had begun to separate and the event rate was 7.3% in the UFH versus 5.5% in the enoxaparin group, corresponding to a 24% relative risk reduction in the primary end point. A stable benefit of enoxaparin was observed through 14 days, at which time the incidence of the primary end point was 16.7% in the UFH group and 14.2% in the enoxaparin group (figure 3).

Approximately 60% of the patients in the acute groups progressed to the out-patient phase of the study. Although the early benefit of enoxaparin was sustained up to 43 days, during the out-patient phase the two Kaplan-Meier curves remained parallel, indicating lack of additional treatment benefit during the out-patient phase. During the first 72 hours there was no difference in the incidence of major haemorrhage between the two groups, but during the out-patient phase the rate of major haemorrhage was significantly higher in the enoxaparin (2.9%) than in the UFH (1.5%) group. The TIMI 11B results indicate that enoxaparin is superior to UFH for the acute management of non-ST elevation ACS and this superiority is achieved without an increase in major haemorrhage; that treatment should not be continued after hospital discharge.

When the data from TIMI 11B and ESSENCE were pooled in a meta-analysis,[21] a 20% reduction in the composite end point of death and ischaemic events was apparent at 48 hours with enoxaparin, which persisted up to 43 days' follow-up. This apparent superiority of LMWH over UFH must be viewed with caution because in some 40% of patients in ESSENCE and in more than 50% of patients in TIMI 11B, aPTT values were not in the therapeutic range. Furthermore, both these early trials were conducted before the results of FRISC II,[22] propounding the benefit of an early interventional approach, were published: consequently, only 13% of enrolled patients underwent PCI. The results of TIMI 11B and ESSENCE are therefore really only applicable to conservatively managed patients.

A post-hoc subgroup analysis looking specifically at the patients who did not undergo PCI in TIMI 11B and ESSENCE showed a clear advantage with enoxaparin over UFH for the end points of death/MI and death/MI/urgent revascularisation at 43 days, with a small advantage persisting at one year.[23] Therefore, in patients with NSTEMI managed conservatively, the benefit of enoxaparin over UFH seems clear.

## LMWH in ACS with PCI

Post-hoc subgroup analysis of those patients who did undergo PCI during the initial hospitalisation period in the TIMI 11B and ESSENCE trials showed that those treated with enoxaparin experienced significantly fewer clinical events (death or MI) at one year compared to those receiving UFH.[23] The incidence of major haemorrhage was similar in the two groups, although the incidence of any haemorrhagic complication was higher with enoxaparin as a result of more frequent minor haemorrhage (mainly attributable to ecchymoses at the injection site).

Subsequently, FRISC II, TACTICS and RITA 3 established the role of PCI in the management of ACS. The findings of FRISC II (Fragmin and fast Revascularisation during Instability in Coronary artery disease)[22] using dalteparin and the TACTICS-TIMI 18 trial (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy)[24] suggested that an early invasive strategy was indicated if patients had ischaemia on the ECG or raised biochemical markers of myocardial damage.

In RITA 3 (Randomised Intervention Trial of Unstable Angina 3),[25] some 1,800 patients with UA/NSTEMI were randomised to either an early interventional strategy with angiography and revascularisation within 72 hours or an initial conservative approach. All patients received enoxaparin for 2–8 days. At four months, the incidence of death, AMI or refractory angina was 9.6% in the interventional group and 14.5% in the conservative group. This difference, mainly attributable to a halving of refractory angina in the interventional group, persisted up to two years' follow-up. Bleeding events occurred in 4% of the conservative group and 8% of the interventional group, and among the latter, over two-thirds of the bleeds were arterial access or wound site-related. The incidence of haemorrhage was low in both arms of the study, with fewer than 1% of patients requiring non-CABG-related transfusion.

Therefore, although a trial prospectively comparing LMWH with UFH in ACS, specifically in patients proceeding to PCI, has not been performed, the available data indicate that LMWH are a safe and effective alternative to UFH in these patients. The ongoing large-scale SYNERGY (Superior Yield of the New strategy of Enoxaparin, Revascularisation and GlYcoprotein IIb/IIIa inhibitors) study will compare enoxaparin and UFH directly in 8,000 high-risk patients with non-ST elevation ACS likely to undergo PCI.[26]

## LMWH and GPIIb/IIIa inhibitors

### LMWH and abciximab

Most of the trials reporting on the benefits of GP IIb/IIIa receptor antagonists in ACS used UFH. Given the magnitude of reduction in events reported in ESSENCE and TIMI 11B with LMWH over UFH, it is tempting to speculate that the reported quantitative benefits of GP IIb/IIIa receptor antagonists might have been modified had enoxaparin rather than UFH been used. Use of enoxaparin as control treatment might have reduced the event rate in the control arm and therefore reduced the treatment effect of GP IIb/IIIa receptor antagonists; it is, however, also possible that the effects of enoxaparin and GP IIb/IIIa receptor antagonists might have been synergistic.

The National Investigators Collaborating on Enoxaparin (NICE) enrolled patients undergoing elective or urgent PCI for ACS into several studies.[27] NICE 1 patients received enoxaparin 1.0 mg/kg intravenously at PCI; NICE 4 patients received enoxaparin 0.75 mg/kg intravenously five minutes prior to an intravenous bolus of abciximab (0.25 mg/kg), immediately preceding PCI and followed by an intravenous infusion of abciximab for 12 hours. Neither UFH nor enoxaparin was administered following PCI in either study.

The incidence of minor haemorrhage and the need for transfusion were similar in NICE 1 and 4. At 30 days, the primary end point of major haemorrhage had occurred less frequently in the group receiving abciximab in addition to enoxaparin, compared to those receiving enoxaparin alone. This was offset, however, by a higher incidence of severe or profound thrombocytopenia in NICE 4 compared to NICE 1 (0.8% *vs.* 0.0% and 0.4% *vs.* 0.0%, respectively).

The incidence of major and minor haemorrhage in NICE 1, using enoxaparin, was comparable to that seen in the EPISTENT study of patients allocated to stenting plus UFH.[28] This would further support the notion that the use of LMWH is as safe as the use of UFH during PCI. Furthermore, the occurrence of death, MI or urgent revascularisation was also similar in the EPISTENT-UFH group and in NICE 1, implying that enoxaparin and UFH have similar efficacy profiles in reducing periprocedural events following PCI.

Similar retrospective, post-hoc comparison of the NICE 4 results with earlier data from the EPILOG[29] and EPISTENT trial patients receiving abciximab plus low-dose UFH reveals similar frequencies of major bleeding and ischaemic end points in these cohorts, indicating similar efficacy and safety profiles for enoxaparin and UFH when used in conjunction with GP IIb/IIIa blockade during PCI.

Although most data relate to enoxaparin, dalteparin may also be used in combination with abciximab. In a substudy of the GUSTO IV-ACS trial, the combination of abciximab with dalteparin for five days was as safe and as effective as using UFH for 48 hours with abciximab.[30]

### LMWH and other GP IIb/IIIa inhibitors

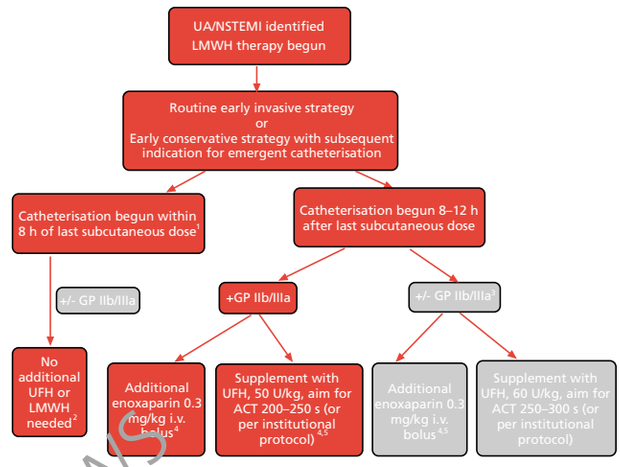
The NICE 3 study examined the use of enoxaparin in 600 patients with ACS in combination with one of three available GP IIb/IIIa inhibitors. Pre-publication results presented at the XXII European Society of Cardiology meeting revealed that the combination of enoxaparin and GP IIb/IIIa blockade was associated with bleeding and ischaemic event rates similar to those seen in earlier studies using the combination of UFH and GP IIb/IIIa inhibitors, implying that this combination is safe and effective, although this was a retrospective comparison.

In high-risk ACS patients receiving eptifibatide, the incidence of major haemorrhage or ischaemic end points at 30 days was significantly reduced by coadministration of enoxaparin compared with UFH in the INTERACT trial (INTegrilin and Enoxaparin Randomised assessment of Acute Coronary syndromes Treatment trial).[31]

Similarly, in NSTEMI/UA patients treated with tirofiban and randomised to enoxaparin or UFH in the ACUTE II study, the incidence of death or MI was similar in the two groups at 30 days, but refractory ischaemia requiring urgent revascularisation was much more frequent in the UFH group.[32]

To guide the transition from medical therapy to procedural anticoagulation using LMWH in non-ST elevation ACS patients proceeding to PCI, with and without GP IIb/IIIa inhibitors, an international task force published recommendations in late 2002, which are summarised in figure 4.[33]

**Figure 4.** Strategies for the transition from medical therapy to procedural anticoagulation in patients receiving LMWH




1. For PCI, wait at least 30 to 60 minutes after subcutaneous (sc) injection, depending on molecular weight of the agent (30 minutes for enoxaparin, 60 minutes for dalteparin)
2. Insufficient data are available to guide heparinization in patients who have received only 1 dose of sc LMWH
3. Fewer data are available on patients treated with sc enoxaparin and no GP IIb/IIIa receptor antagonist undergoing PCI
4. If the patient has been receiving dalteparin, switch to UFH, as there are no available data on transition from medical to interventional therapy when the last sc dose of dalteparin was given 8 to 12 hours before PCI
5. Consideration can be given to enoxaparin 0.5 mg/kg in those patients not receiving concomitant GP IIb/IIIa receptor antagonist therapy

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**Key messages**

- Low molecular weight heparins have pharmacological benefits over unfractionated heparin
- Low molecular weight heparin or unfractionated heparin are recommended for the treatment of non-ST elevation myocardial infarction unless coronary artery bypass surgery is planned within the next 24 hours
- Evidence supports the combination of enoxaparin and tenecteplase in those under the age of 75
- The role of low molecular weight heparin in primary or rescue percutaneous coronary intervention is as yet undefined

## Conclusion and recommendations

The 2002 ACC/AHA and ESC guidelines for the treatment of non-ST elevation ACS list the use of either LMWH or UFH as a Class I recommendation (level of evidence, A) but recommend the use of enoxaparin over UFH (Class IIA, level of evidence, A) unless coronary artery bypass surgery is planned within the next 24 hours.[34] LMWH may be used alone or in combination with GP IIb/IIIa inhibitors in the setting of PCI. Several studies indicate that this approach is safe and effective, although the 2002 guidelines do not discuss the role of LMWH in PCI, pending the results of ongoing trials.

In STEMI treated with pharmacological reperfusion, evidence supports the combination of TNK with enoxaparin in those under 75 years, for reasons of efficacy and speed of administration. In the setting of primary or rescue PCI, the role of LMWH remains undefined and UFH, with or without GP IIb/IIIa inhibitors, should continue to be used.

However, limitations to the benefits of LMWHs persist. They are unable to inactivate fibrin-bound thrombin, which may be an important trigger for clot extension at sites of vascular injury. Further trials with new antithrombotic drugs such as direct thrombin inhibitors, factor Xa inhibitors and tissue-factor-pathway inhibitors are awaited.

## Conflict of interest

None declared.



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